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# EMERGING PROBLEMS FOR THE PEDIATRICIAN*

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To discuss, in the midst of a global war, the problems of the Country's small children may seem ill-timed. With the exception of a few leaders, those who now have spread war and hatred everywhere were children during the last war. It is at least possible that the pediatrician of today can perform a service for peace that will equal that of any other person. Not that there would be any wisdom in our raising our sights to that level today. I am sure that the problems discussed are of importance to the whole field of pediatric practice, but it would be ridiculous to think of them as having more than an indirect bearing on our next great task—that of winning the peace.

Every child comes into the world to carry on a certain pattern. We, you and I, are accustomed to continuity in the history of the organism. We see the 8-year older in terms of when he was 6. We are making considerable progress in the converse of this—that is, we are making more and more reliable assays at 6 as to what this child will be when he is 8 or 18. But the matter runs beyond this and the physician, individualist that he is, is not too hospitable to this extension. He doesn't like to realize that months before the child was born the family hoped it would be a girl or hoped it would be a boy, not having the courtesy to await its birth before fixing upon it the pattern they hoped to be continued. He does not like to realize that years before the child was born, often years before the marriage occurred, there were inexorable grooves being planned for it. So much of what we could see if we wanted to is not in the child or of his making but only in the fact that that differs from what the parents just had to have him live.

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Nor are these demands to be swept away with a wave of the hand. They are made of unbending family tradition, of faults or frustrations in the parents' own earlier life, of the most insistent dreams of goals, of neighborhood and cultural pressures. One never just brings up a child, but rather brings him up in terms of all of the history and all of the present status of the parents' life. Because these other things antedate the child and because he is so soft and helpless we bring him up *to* these family and cultural patterns.

I have insisted upon this because if you are going to treat children instead of the diseases of children such a large part of your work will lie precisely in this field of understanding what each child was *meant* to be. That doesn't perhaps have too much to do with his catching measles, but it has everything to do with the anxious, over-solicitousness or the slovenly neglect which mark the course of that illness. And it has everything to do with feeding problems, persistent enuresis, stubborn negativism, temper tantrums or quiet conforming mask-like politeness, carefree adventure or timorous fear, in a word with all that host of personality and behavior reactions that are each day a larger and larger fraction of your practice. This I am choosing to term not an emerging problem for the pediatrician (though it probably technically is so) because it is no more than a basic point of view as to your work which underlies some five things that in our generation are sweeping through this whole matter of the formation of these family patterns. The person whom we fondly term "the family physician," he who preceded our present days of insistent specialization, probably saw each member of each family in terms of what that family was trying to live out through him. I would say to today's pediatrician that he must recapture that point of view. And the emerging problems are those specific difficulties that he will find belonging to the family of this generation.

(1) One of these stems from the very rapid decrease in the size of the American family. There are two quite distinct aspects to this. The first is the disappearance of the clan group. A good fraction of us here this afternoon grew up in a household abounding with grandparents, aunts, uncles and

other addenda. Various factors have pressed toward lessening the size of the household and we must see how much more of a "load" this puts on each member. Love, humor, tolerance, patience, righteous indignation, sharp demand that duty be done, softness—it is impossible that two or three can give all this picture where seven, eight or ten found it so much easier. One does not know how long this will last; perhaps down through the ages this small intimate group will continue to impose an intolerably complex and heavy load on each of its members. I am sure that, with me, you are constantly struck by the loneliness of people, by their need for reassurance, by their request that you stand by them in their troubles much more than that you help them with these troubles. I *think* that a large part of all this last picture comes from the dramatic disappearance of the clan household. The Depression and the War have reversed the trend, but I think that we are fair in assuming that this is a temporary change.

The other aspect of this matter of smaller families is that of fewer children in each marriage. This, in shorthand terms, has made each child more precious. It is so easy to say to the mother that she worried about too many things, that she is over-anxious. But are we being realistic here? Whether we like it or not must we not resign ourselves to these complications for as long as parents have but one or two children into whom must be poured all their hopes? You might gaily set out to advise larger broods of children, but I don't believe that you will get very far.

(2) One never falls in love with a real person. Those we care for the most deeply we idealize the most intensely. This intolerance challenges us always to that love that is so deep and so real that its bonds hold as the loved one turns out to be a real person. What havoc this plays with family life! How many husbands go bitterly through life endlessly trying to make of wives what they *thought* they were! How many mothers refuse to succumb to the "defeat" of allowing a child to be himself, a real person, instead of just what he was planned to be!

One speaks of this in March of 1945 because it is for now a problem of unusual magnitude. A woman may be so unselfishly gracious—if you don't have to live with her! A man so tenderly brave! The War means that there are millions of young families where now for many months an idealization (husband, wife, father, child, etc.) is occurring that actuality can in no way match. This will all come to your doors in varying form. For instance, there certainly will be a sharp rise in divorces following the War. It is going to be said as to these that they are the result of a "cooling off" process. That will be true of many, I agree. What it is necessary that you see is that in large part the dynamics of the situation will be precisely the opposite to this. And what stubborn problems of adjustment are going to come to you as returning fathers or reunited families attempt in some dazed fashion to fit reality to the unbridled dreams of these many months of separation.

(3) Education has undergone an interesting development in this Country. Through our own history we have constantly urged more education as the solution to any social ill. However, it has been largely in our generation that education has become also a badge of social position. We go so and so far in school if that is the place to which "most of the group to which we belong" goes. This tremendous pressure toward school success as the badge of the family's position is relatively new. I doubt if many pediatricians have any conception of the rigidity of the stratification which this imposes upon the child. If he is 8 he must be in third grade, and with what auxious eyes he compares his grades with the one whose birthday is two months ahead or behind his! If I point out to you that this is the source of innumerable disturbances in the higher reflexes (speech, nausea, sphincter control, and later, sex) it is not to ask you to become specialists in education. However, I don't believe that you can treat the child (as opposed to just his diseases) unless you have a very fair understanding of the importance of and limitations of the I. Q. and unless you know the general demands of the child's school. Are those he competes with of average or superior or inferior ability? May I take a moment to point out a specific applica-

tion of this emerging problem. The child with an I. Q. of 75 will come to you with fewer problems in this area of the higher reflexes than will the child with an I. Q. of 90. The former is more handicapped, it is true. But his handicap is marked enough to set him apart and to allow a tacit adjustment to his difficulty. The child with the 90 I. Q. can never rest. He is low enough so that it is a constant struggle to keep up with the average ones yet high enough so that allowances are not made for him.

(4) Few things will nettle you more than the growing sophistication of today's parents. How their "knowledge" rolls from glib tongues! It requires fast foot-work not to be counted out—the victim of this or that withering question as to one's adherence to a favorite theory as to behavior. This distressing situation has so interesting an origin that I cannot refrain from an aside as to its development. Determinism was accepted in the physical sciences many years ago, everything that happens has a discoverable cause. Psychology, in its effort to legitimacize itself amongst the sciences, adopted determinism and bravely set out to give the cause for every bit of conduct. It soon ran into trouble due to the complexity of the problem; many, even very important, things just didn't seem to have any discernible cause. To meet this distressing situation an assumption was made of the unconscious. I am not trying to say that the unconscious does not exist. Nor have I the slightest objection to any one's using it to explain any conduct or traits as long as he understands that that is what he is doing. So far as I know it, no one has ever experienced the unconscious. Any one who "explains" to you how the unconscious works goes no farther than to say "These are the simplest and most direct assumptions which I can make as to the origin of such and such." By all means, if there is the time, familiarize yourself with the formulations of the leading psychoanalytic schools of thought and with other theories as to behavior. But, failing this, remember that most children are pretty direct in their communication and that if you will patiently and humbly try to figure out what they are trying to tell you when they wet the bed or play truant (instead of just trying to do away with

these bits of behavior), it won't be often that you need to trouble over the complicated questions of their parents. At that it remains a tough problem; the lay public avidly reads each new promise of understanding and rushes to your office in a most embarrassing show of exhibitionism. Assailed here on every side, I wish you luck!

(5) I have long been interested in the problems arising from the high mobility of our people. I am not a competent observer because I see only a part of the picture. If I say that it produces serious insecurity in children who never get a chance to take root solidly, I must admit that these are the only ones whom I see. How many Americans have been toughened by this, how many have developed internal resources of strength and completeness, I haven't the slightest idea. If we are discussing emerging problems then it is proper to enumerate among them the fact that America is on the move as perhaps never before. This is not the Grand Western Migration of those fit for the venture, this is not the urban concentration of those who are looking for that experience. Willy nilly, catholic in its touch, this movement is involving a large fraction of our population, and for better or for worse, you will see the results of it. I suspect that you, as I, will record the panic of children, their lack of sure-footedness, their marked dependence on their mothers as the only constant element in their environment. However real that phenomenon will be, we must not forgt that it will be *that type* of child who will come to us for help. Perhaps by the very nature of his calling the physician can never make a fair assay of the positive as well as the negative contributions of this so typical American phenomenon of high mobility.

If there, then, are five emerging problems for the pediatrician of today, what is he to do about them? In interested fashion shall we just look them over in the lighted show-case, or are they to be a functioning and dynamic part of our actual practice? About this I should like to say some things.

(1) I would hope that you will see that change and growth produce tensions. When little Mary breaks long cherished toys it is because now she is strong enough or has well integrated

enough mechanisms to do so. We look back upon periods of man's development to see what perplexities these brought. Why have we so little faith that our present troubles are but part of further growth. Growth to what? I don't know any more than you. Yet I think that it is fair to point out that man has a tremendous potential toward adjustment, and that we have as much right to see our present uncertainties as part of a move toward some higher integration as in any other light.

(2) These matters, and their like, you must see as "complications" of any illness you are called upon to attend. Being physicians, poorly, if at all, trained in this area, it will be inviting to say that all of this is none of your affair. I assure you that here are considerations that will intrude themselves, whether you wish it or not, and that you will be forced to see each sickness *in the light of* these tensions.

(3) As you are forced into this field of emotional interaction you will come to an entirely new relationship to the phenomenon of frustration. Frustration is now perhaps your most constant ally in the purely physical area. The full stomach demands that the child eat no more; anemia wisely produces lassitude, and the hypothyroid just as wisely appears as the "lazy" child. Note that frustration within a highly organized entity thus does yeoman's work in prevention and therapy. But what of frustration in the social area? When you are asked to keep the child from stealing, note that the primary purpose is the comfort of *society*, not that of the child. If we exhort to sexual continence it is in the name of a better integrated body politic. I am not for a moment arguing against these interpersonal barriers and frustrations. I think that many pediatricians have rather naively seen them, however, simply as extensions of the helpful devices of a friendly ally. They are necessary but they become each day more and more disturbing complications rather than aids.

(4) As we move into this field of social interaction, I'd feel it more realistic to say that as we are forced into it, there will be no more perplexing problem for the pediatrician than that as to who is his patient. The distraught or confused or battling parents will come to you to "cure" the night-terrors of the child.

The pushing parents will want you to stop the enuresis of the child whom they are endlessly prodding to high scholastic attainment. Will you be just one more adult to make impossible demands on the little one or are you to be ready to alter the lives of those who bring him helplessly to you and who pay the bill? The psychiatrist does not presume to give the answer, that is for each one of you, for yourself to decide. I can say that, no matter how difficult, the decision must be made and must be a part of every day's labors.

(5) Those of you who have looked at all into psychiatric ventures in the area of people's living together must be amazed at the variety quite as much as the intracacy of our theory and practice. Who is right? Freud, Meyer, a baker's dozen of others? Which is the white-haired one? May I point out that all of this variety is not so imposing and challenging as the startling fact that each of these theories works beautifully. What are we to do with the fact that every school of therapy has had quite remarkable success? As I see it this can mean only one thing, that it is the fact of contact rather than the content of that contact that is the important matter. In the midst of change and tension nothing presses on us more than the loneliness and feeling of helplessness of people. That for awhile we walk along a little way with them; this, I am sure, is more and more the critical point in therapy. Call it reassurance if you will, what parent and child seek most is that for awhile we see their ventures through their eyes, and that we care. There can be no other answer to the fact of relative success for so many and so diverse approaches to these complicated problems.

# DIAGNOSIS OF HOSPITALIZED PATIENTS

PAUL ROCKWELL*

This is a study of possible correlation between proposed diagnoses and findings in 100 consecutive postmortem examinations of patients who died while under the care of the staff of the Department of Internal Medicine in the John Sealy Hospital. It is not a complete survey of the diagnostic success of the members of the Department, since it deals only with conditions which were serious enough to have been contributory to the patient's death. The fact that all of the patients in the series died does not necessarily imply a disproportionate number of wrong diagnoses, since in only one of the 100 cases could it be said that the patient's death was probably directly connected with his being incorrectly diagnosed.

The chief significance of this survey may lie in the indication of the trend of diagnostic perspicacity exercised by the Department staff. Because the conditions listed are those which probably were directly concerned in the fatal outcome, many findings such as small pulmonary infarcts and patches of bronchopneumonia which were quite frequent and probably of little clinical significance, were not included. In some cases it is difficult to tell from the pathologist's description just how extensive such a process has become and conclusions have to be reached by carefully sifting all the clinical and pathologic information.

Postmortem examination of the 100 patients showed 154 conditions which were considered to have been of significance. Upon admission, 19 diagnoses had been definitely established as indicated in the records of previous admissions. Twelve new conditions had developed in these same patients by the time of their last admission; in only 3 instances were they correctly diagnosed. Of the 9 incorrect diagnoses, 4 probably could be attributed to failure to continue careful search after finding an

*From the Department of Internal Medicine, The University of Texas School of Medicine, Galveston, Texas. Received for publication May 1, 1945. Read at the March, 1945, Hospital Staff meeting.

established diagnosis. Two patients had pulmonary tuberculosis; one had tuberculous meningitis and another had an enlarged heart and an aortic aneurysm not mentioned in the previous rather sketchy physical examination. In one case, arteriosclerotic heart disease developed undetected, a large pulmonary infarct, and in a case of rheumatic heart disease the patient died of lobar pneumonia which had not been discovered.

### Examination of the Patient

Of the 154 diagnoses, 47 (30.5 per cent) were considered to be definite after the history and physical examination were recorded. In this group were mostly hypertensive heart disease, some cerebrovascular accidents, a case of acute pericarditis and others where the story or physical signs can be said to have been definitely diagnostic. In 47 more cases, the history and physical examination were suggestive and led to studies which brought out the correct diagnosis. Therefore, most of the 104 correct diagnoses (90.3 per cent) were directly related to a contributory history and physical study. The importance of this is further shown by the fact that 22 (44.0 per cent) of the 50 wrong diagnoses were in patients who had either inadequate history or physical survey or both. Lack of a satisfactory history and physical examination is contributory to poor diagnosis. Nevertheless, such lack does not necessarily imply defection on the part of the house officers, since 8 of the 17 patients who had poor history or physical recordings either died within three hours of admission or were too moribund to give a history or permit thorough physical examination to be made.

Table I shows the diagnostic status of the patients on the basis of the previous record, as a result of examination of the patient, or following a new condition which developed during the patient's stay.

On admission, presumably 123 conditions were present which had not been diagnosed on previous records. Of these, 67 (54.4 per cent) were correctly stated on the admission impression. During the hospital stay, 9 of the errors were corrected, raising the percentage to 61.7. This figure was not substantially

TABLE I

Showing diagnostic status of patients as revealed by postmortem examination

| | Correct | | Incorrect | |
|---|---|---|---|---|
| A. Admission condition ..... | 86 | | 56 | 142 |
| 1. Previous record ..... | 19 | | | |
| 2. History and physical examination ..... | 28 | | | |
| 3. Other adm. Imp..... | 39 | | | |
| 4. Diagnosed after adm... | 9 | (—9) | | |
| B. New condition developed while in hospital..... | 9 | 3 | | 12 |
| Total ..... | 104 | 50 | | 154 |

altered by the new conditions which developed while the patient was in the hospital; 9 were correctly diagnosed and 3 were missed. The percentage of correct impressions was thus raised from 54.4 on admission to 62.9 on discharge. The percentage of all diagnoses considered to have been definite or highly probable on admission (including old record diagnoses) had, however, more than doubled, rising from 33.0 on admission to 67.5 at the time of discharge.

The most interesting fact about the diagnoses made on admission is that when the old, established diagnoses, and those which were definite from examining the patient, were removed from the group, only 37 of the 95 remaining conditions (38.9 per cent) were correctly stated on the admission impression. Apparently, when a patient has a condition which is not obvious from old history or from routine history and physical examination, the admission impression is only a rough guide to further study and is more apt to be incorrect than correct.

## CONSULTATIONS

A total of 28 consultations were held on these patients. In 6 (3.8 per cent) of the conditions found at postmortem, the service of the consultant was definitive in the diagnosis. Three of these consultations involved sternal punctures by the Hematology Service. Two biopsies were done, one of a lymphomatous node by Surgery and one of a uterine carcinoma by the

Gynecology staff. The remaining contribution was the finding of a urethral stricture by the Urology consultant in a patient dying of cystitis, ureteritis and pyelonephritis.

Five consultants were in error. Those in Urology and Surgery gave opinions concerning malignancy in a liver which at postmortem showed only chronic passive congestion. In one case, a cardiology consultation discussed tricuspid stenosis which was not found at necropsy. Two patients developed mesenteric thrombosis, and at the time of death the Surgical and Medical Departments were undecided as to the diagnosis, though mesenteric thrombosis had been considered in both cases.

In three cases the patients died before they were studied by the consultant.

These data give little information of value concerning the consultation service of the hospital, since they do not include those patients who were transferred to other services or the many patients whose incidental complaints were attended by consultants. A survey of consultations given or asked by this Department over a certain period of time on all patients, including those transferred on or off the service, might give information to permit suggestions for the betterment of consultation efficiency.

Some data were obtained concerning laboratory work performed or omitted on the patients. These data will be discussed below in connection with the study of diagnostic errors.

## Erroneous Diagnoses

Of the 50 incorrect diagnoses, 14 (28.0 per cent) were on patients who died before they could be satisfactorily studied. So that routine and special studies can be made, a patient must be in the hospital twenty-four hours, and taking into account the inevitable delays, admission impressions often cannot be checked in less than forty-eight hours. It is impossible to look at a patient's chart and tell what small obstacles and special problems will confront the house staff. In these 14 patients, all of whom died within twenty-four hours of admission, the

failure to carry out diagnostic measures is probably excusable. However, in 4 of the 14 patients it is conceivable that energetic application to the problem on someone's part might have brought a closer approach to the truth.

One patient with bronchopneumonia was seen in the emergency room in very poor condition, though apparently able to talk and permit examination. By the time she had reached the ward she was failing rapidly and died ten minutes later. The emergency room record is the only one on the chart and it is too sketchy to permit a diagnosis. One patient came to the emergency room complaining of epigastric pain and vomiting. He was thought to be suffering from coronary angina, but no electrocardiographic studies were made during the three hours he lived. Postmortem examination revealed acute hemorrhagic gastritis. The patient admittedly had been in poor health when seen. However, an electrocardiogram might have led the examiners to look further than the heart for a diagnosis. Another patient died within three hours of admission. Although an informant was available, the short history and physical study gave little clue to the colitis discovered at autopsy. Blood chemistry studies were not made.

One patient died of severe anemia twenty-four hours after admission. No special studies were made to determine the nature of the anemia. At necropsy a generalized hypoplasia of the bone marrow was found. One other patient was in the hospital two days, but probably belongs in this group. He died of carcinoma of the sigmoid but was too moribund to permit roentgen ray study. The other 10 patients died before the correct diagnosis could be elicited.

In 6 more cases the condition under question was obscured by another condition. Three patients who died in congestive failure also had pulmonary infarcts, but the signs in these cases apparently were obscured by congestive failure. One of these patients had portal cirrhosis which also was undetected prior to necropsy.

One patient with carcinoma of the pancreas also had portal cirrhosis. Carcinoma of the pancreas was listed as a secondary diagnosis on admission, but this was apparently discarded and

was not mentioned again. Cirrhosis was correctly diagnosed. The patient died of the combination of the two diseases; still there was no part of the picture which could not conceivably have been due to cirrhosis alone.

Carcinoma of the pancreas was found in another patient who died after three days of moribund incoherence during which he complained of pain in his back. He was known to have had a cerebrovascular accident recently, and aside from the back pain, there was nothing which could not have been explained as being secondary to the deteriorated central nervous system.

There were 3 other diagnoses in which the error could not be called the fault of the attending physician. One patient with cirrhosis died of terminal bronchopneumonia, which, in spite of good progress notes and several chest examinations, was not described on the chart. It is possible that there was difficulty in examining the patient or that signs which might be expected were not found.

A patient with pulmonary tuberculosis was found at necropsy to have had involvement of the meninges. There was no clinical evidence of this, though it was sought before death.

Cerebral hemorrhage developed in the third case while in the hospital. The diagnosis seems to have been on the intern's mind, but he never definitely stated it. He appeared to have been waiting for the neurologists to see the patient. When the patient died before being seen by a neurologist, no statement was made concerning the cerebrovascular accident.

Concerning the remaining 27 conditions found incorrectly diagnosed at necropsy (54.0 per cent of the errors, 17.5 per cent of the total cases), the impression was gained from reading the charts that information had been available which could have led to either a deduction of the truth or to the taking of steps which might have given considerable help toward the right answer. Again, it is difficult to say from looking at a chart whether some special problem might have obtained with a given patient, and as much charity has been exercised as possible.

In 10 (37.0 per cent) of these 27 conditions, the charts showed great lack of descriptive effort in either the admission

work up or the progress notes, and the errors in diagnosis probably can be ascribed to inadequate examination. In the charts of 2 patients whose deaths were related to bronchopneumonia, and in one to a pulmonary infarct, there was no record of chest examination during their hospitalization. One private patient who died of hypernephroma and who also showed cardiomegaly, was in the hospital nine days and no history or physical examination was recorded on the chart.

The condition of another patient who had a preliminary examination and no progress notes, was diagnosed as asthmatic bronchitis. He died twelve days after admission and at necropsy was found to have had pulmonary tuberculosis which had spread to the pericardium.

Meningitis was detected at autopsy in a patient who had died of pulmonary tuberculosis, but there was no record of its having been looked for clinically. Even so, signs of meningitis might not have been found, since, in another similar case, meningitis was looked for clinically and not found.

Another patient with known tuberculosis entered the hospital five days before his death, giving a history suggestive of left heart failure. The physical examination did not describe the heart, but at autopsy the patient showed cardiomegaly and aortic aneurysm.

A private patient known to have asthma, came into the hospital in marked respiratory distress. He spent his four hospital days in an oxygen tent and detailed examination was admittedly poor. There were no progress notes, no roentgen ray examination or electrocardiographic studies made. He was thought to have asthmatic bronchitis. At autopsy toxic degeneration of the myocardium was found, apparently secondary to bronchopneumonia and emphysema. From the postmortem description, the heart condition seemed to have played a fairly important role in the patient's death. The remaining 2 cases fell into other categories and will be discussed below.

In 8 (25.1 per cent) of the 27 conditions, some procedure related to the condition in question was omitted. One patient who died of hypertensive heart disease showed chronic glomeru-

lonephritis at autopsy. During her 3 days of hospitalization no urinalysis was recorded. She may have been anuric, but no mention of that was made on the chart.

Another patient died in heart failure after an acute myocardial infarction. The history was atypical, but suggestive enough that an electrocardiogram was obtained on admission. The graph showed changes indicating old damage, but was not repeated during the ensuing six days that the patient lived. The clinical diagnosis was hypertensive and arteriosclerotic heart disease.

In another case in which there was considerable brown atrophy of the heart, the patient's primary difficulty had been hypoplastic anemia. His moderately severe cardiac difficulty was considered, at the time of entry, to be on an arteriosclerotic basis and not mentioned in the progress notes. No electrocardiogram was made.

A patient with carcinoma of the pancreas was hospitalized for 66 days and no specimen for biopsy was taken although there were several available nodules. However, only exploration would have settled the question of origin.

One patient came in complaining of pain in the upper portion of the abdomen. The gastrointestinal tract was studied, but although she was in the hospital for nineteen days, no study was made of her gall bladder. As the time of death neared, there were signs strongly suggestive of intracranial hemorrhage, and subsequently she contracted pneumonia which was correctly diagnosed. Cranial exploration was not permitted at autopsy. The only apparent explanation for her complaint at time of admission was cholelithiasis and chronic cholecystitis.

Another patient who was a known diabetic, was admitted in a confused mental state which did not clear up during her twenty day stay in the hospital. She complained of vague abdominal pain, frequent vomiting, and swelling of the abdomen and legs. On physical examination she was found to have considerable ascites. She was thought to have hypertensive and arteriosclerotic heart disease, and although the venous pressure in her arms was not elevated, this diagnosis was not changed. Obesity prevented complete pelvic examina-

tion. Routine examination and studies were fairly satisfactory except that when an abdominal paracentesis was performed, the fluid was not saved for histologic examination. She was thought at one time to have an intestinal obstruction. An obvious cerebrovascular accident occurred shortly before death. At discharge, the diagnosis was diabetes, hypertensive and arteriosclerotic heart disease, possible intestinal obstruction, cerebrovascular accident and tuberculous peritonitis or peritoneal malignancy—origin not specified. At necropsy, widespread carcinomatosis was observed in the ovary. The intestinal obstruction was not determined. The heart revealed only toxic degeneration. The cerebrovascular accident was found to have been correctly diagnosed.

In 5 cases the data necessary for making the correct diagnosis was available, but the diagnosis was not written in the chart. One patient entered the hospital in the terminal stages of malignant hypertension. The intern's admission impressions were pernicious anemia, gastro-intestinal bleeding and nephritis. Malignant hypertension was fourth in his list. The next day the resident made the correct diagnosis. No mention in progress notes or discharge summary was made of the diagnosis of luetic aortitis which had been established on a previous admission.

The symptoms of one emaciated patient, who was in respiratory distress and showed signs of pulmonary infection, were correctly diagnosed as bronchopneumonia with the additional impression of malnutrition. He was in the hospital three days, but there is no evidence on the chart that the old record was examined, and no reference was made to moderately advanced portal cirrhosis which had been diagnosed previously.

Two patients entered the hospital in congestive failure resulting from hypertensive heart disease. The urine of both showed albumin, casts and low specific gravity. Heart disease was correctly diagnosed and treated accordingly, but no reference in the physical examination at admission or in the progress notes was made to kidney disease. At autopsy both patients showed fairly advanced arteriolar nephrosclerosis.

Another omission occurred when a patient with a saddle embolus eventually developed a pulmonary infarct. Both of these conditions were accurately diagnosed, but the myocardial infarction, which seems to have been the starting condition, was not mentioned. It may have been thought of since an electrocardiogram was taken on admission. However, it did not show definite evidence of recent myocardial damage, and was not repeated. Myocardial infarction was not mentioned on the chart.

In 6 more cases the history and physical examinations were quite suggestive, but the correct diagnosis was not mentioned in the differential diagnosis. These included the case of a patient with bronchiectasis and bronchopneumonia, called asthmatic bronchitis, who died two days after admission; a patient in congestive failure whose enlarged liver led to a two months' search for malignancy but who, at necropsy showed only chronic passive congestion; a patient with carcinoma of the pancreas, admitted with the diagnosis of gastric malignancy and discharged with the impression of hepatoma, wherein the correct diagnosis was not mentioned on the chart; a man with unresolved pneumonia and pulmonary abscess in addition to arteriosclerotic heart disease, in whom a brief physical examination resulted in a diagnosis of carcinoma of the stomach with metastases to the lung; a patient with uremia who was thought to have had an intracranial hemorrhage because of terminal hyperpyrexia, but in whom necropsy revealed only uremic swelling of the brain; a patient with leukemia in whom liver infiltration had become extensive died of ruptured esophageal varices, the possibility of which was not brought up clinically.

In evaluating these 100 cases as carefully as possible, and recognizing the difficulty associated with the position from which such a viewpoint is taken, an effort has been made to note how many of the patients died because their conditions were not correctly diagnosed. Of the 100 fatalities it can be said that only one probably would have recovered had the correct diagnosis been made. This was the case of a 63-year-old man who was known to have had rheumatic heart disease and who had been fibrillating for about two years. He was irregular-

TABLE II

Analysis of Reasons for Unsatisfactory Diagnoses

| | Number | Per cent of wrong diagnoses | Per cent of total diagnoses | Per cent of cases which might have been diagnosed |
|---|---|---|---|---|
| 1. Total wrong diagnoses.... | 50 | | 32.5 | |
| 2. Died in 24 hours..... | 14 | 28.0 | 9.1 | |
| a. Conceivably might have been diagnosed ..... | 5 | 10.0 | 3.2 | |
| b. Died without clue..... | 9 | 18.0 | 5.8 | |
| 3. Condition obscured by other condition ..... | 6 | 12.0 | 3.8 | |
| 4. Miscellaneous ..... | 3 | 6.0 | 1.9 | |
| 5. Might have been diagnosed ..... | 27 | 54.0 | 17.5 | |
| 6. Inadequate H or P..... | 10 | 20.0 | 6.4 | 37.0 |
| 7. Procedure omitted ..... | 8 | 16.0 | 5.1 | 25.1 |
| 8. Data necessary present... | 5 | 10.0 | 3.2 | 18.5 |
| 9. H and P suggestive but diagnosis missed ..... | 6 | 12.0 | 3.8 | 22.2 |
| 10. Probably would have recovered ..... | 1 | 2.0 | .64 | |
| 11. Probably would not have recovered ..... | 47 | 94.0 | 30.5 | |
| 12. Recovery problematic .... | 2 | 4.0 | 1.3 | |

in his attendance at the heart clinic and at least twice he had gone for several days without taking digitalis. He had never, however, shown signs of frank congestive failure. On admission he was not clear mentally, but said he had omitted taking digitalis for two or three days a week because he had felt nauseated; he had taken it daily, however, for the three days prior to admission. The onset of symptoms was not described and the patient was presumably too incoherent to give a reliable story. He was cyanotic and in obvious respiratory distress. No mention was made of a cough. The rheumatic heart disease was elicited on physical examination; the liver was enlarged; neck veins pulsated, but there was no peripheral edema. The description of the lungs is quoted in its entirety "moist rales in bases, ant. and post." The patient was con-

sidered to be in failure and was treated accordingly. His temperature remained elevated, and he died forty hours after admission. At autopsy evidence was found of lobar pneumonia in the left lower lobe and bronchopneumonia throughout the right lung. Since he not only was seriously ill but was a cardiac also, he might not have survived even with proper therapy; however, it seems reasonable to classify this case as one in which the patient probably would have recovered if his symptoms had been accurately diagnosed.

There were two patients who might have recovered, but their condition was such that recovery can only be speculated upon. One of these was a 47-year-old colored man who had had mild shortness of breath and ankle edema for six to eight weeks. He had been digitalized, but it caused him to become intoxicated so he discontinued the medication of his own accord. Since stopping the digitalis the edema had increased to 4 plus, and on admission it was up to his hips. He had had typical paroxysmal nocturnal dyspnea and orthopnea for two weeks. There was polyuria at the beginning of his illness, but it had subsided and he had passed very little urine for three or four days. He had a sharp pain in his chest four days before admission, followed by bloody sputum.

Physical examination revealed him to be very dyspneic; his blood pressure was 170 systolic and 60 diastolic; there was marked pericardial friction rub and paradoxical pulse; there was dullness over part of the left lung and many rales in both lungs. Uremia was suspected on the basis of arteriolar nephrosclerosis in spite of a non-protein nitrogen which was reported as 50 mg. per cent. Conservative methods were employed to stimulate urination, but were unsuccessful, because the bladder never was palpable he was not catheterized or subjected to cystoscopy. He became moribund and died forty-eight hours after admission. At autopsy the ureteral orifices were found to be partially occluded by papillary adenocarcinoma of the bladder. It is possible that ureteral catheterization might have prolonged his life although the ultimate prognosis was very poor.

Another patient with known heart disease was admitted to the hospital with the chief complaint of pain in his chest and increasing weakness for two or three days. There were rales at the bases of both lungs. The venous pressure was 5 cm. The blood pressure was 80/50. The specific gravity of urine was 1.009 in a specimen taken while he was dehydrated. Non-protein nitrogen was 53 mg. per cent on admission and rose to 74 mg. per cent before death two days later. Uremia was suspected. While in the hospital he did not receive digitalis or sulfa drugs. At necropsy two days after admission, the heart showed moderately advanced arteriosclerosis. The kidneys were sclerotic, but appeared to be capable of function. Both lungs showed chronic passive congestion and advanced bronchopneumonia.

If this patient was a cardiac he should have been given digitalis. The advisability of administering sulfadiazene to a man suspected of having uremia is open to question, but in this case the extensive bronchopneumonia, although not described in the very short physical examination, was more serious than the fairly good kidneys. The terminal loss of kidney function was, quite possibly, a result of systemic conditions secondary to heart failure and pneumonia. As with the previous patient, the possibility of recovery can only be speculated upon.

## General Observations

The most frequent condition found in this series of patients (19 per cent) was hypertensive heart disease; next, (13 per cent), some form of intracranial hemorrhage, and third (11 per cent), pulmonary tuberculosis.

In 52 per cent of the cases, 2 or more significant conditions were discovered at autopsy. Of these 52 cases, 19 (36.5 per cent) had complete clinical diagnoses; 29 (55.7 per cent) of the diagnoses were partly correct, and 4 (7.7 per cent) were entirely wrong.

Carcinoma of the pancreas was present in 4 patients and was not correctly diagnosed in any case. In only one case was it suggested; this was later and apparently was discarded

in favor of the diagnosis of portal cirrhosis. The patient actually had cirrhosis, but he also had carcinoma of the pancreas with extensive metastases to the liver. One other patient who entered the hospital in a moribund state has been described above. In the other 2 patients there was considerable involvement of the liver by metastases, but no jaundice; pancreatic carcinoma apparently was not considered, at least it was not mentioned.

The necropsy reports left a great deal to be desired in many cases. Such phrases as "areas of encephalomalacia" in the brain or "an infarct" in the lung were frequent and it was at times impossible to tell from the description how extensive or how recent a process had been. Careful description sometimes was sacrificed for brevity, particularly in relation to the heart and lungs. One patient who died of mesenteric thrombosis, had been fibrillating during life. At autopsy the heart was enlarged and in the summary was listed as cardiomegaly, but the coronary arteries were not described, and the cardiac condition had to be listed here as "cause unknown."

## Summary and Conclusions

1. The charts of 100 patients were studied after post-mortem examination. Of the 154 conditions considered to have had a bearing on the fatal outcome, 67.5 per cent were correctly diagnosed.

2. The grave importance of careful history-taking and physical examination have been emphasized by these figures.

3. This study emphasizes the fact that as long as a patient is under our care we must never relax our attention toward him nor fail to make use of all available data to avoid intervention of the unforeseen, the unusual and the overlooked.

# THE WEIL-FELIX TEST IN PREGNANT WOMEN

## Preliminary Report

Weldon C. White*

Gratch (1943) reported that Proteus OX–19 was agglutinated by all the sera of 505 pregnant women when tested by the rapid slide agglutination method. Of 288 sera from non-pregnant women none were positive. Fifty sera from pregnant women were tested by the standard test tube method of the Weil-Felix test with titers ranging from 1–256 to as high as 1–1,024.

In connection with a survey of the incidence of the positive Weil-Felix test in the general population underway in this laboratory, the standard test as described by Felix (1944) was run on 103 sera sent to the clinical pathology laboratory for routine Wassermann test and on the sera of 43 women in various stages of pregnancy (from 3 months to just before delivery). The diagnoses of pregnancy were made clinically in the obstetrics and gynecology clinic of this hospital. The highest dilution of each serum which gave an agglutination visible without the aid of a lense was considered positive. The results are shown in the accompanying table.

It will be noted that there are many more positive sera among the pregnant women; however, most of them were of very low titer and would not be considered as significant so far as the diagnosis of typhus fever is concerned. In almost all cases the agglutination was weak, usually 1 plus to 2 plus. Among the routine Wassermann sera, 3 or 2.7 per cent were positive to a significant titer of 1–160, indicating a possible past typhus fever infection. Although only a small number of sera of pregnant women were run, a similar percentage of 2.3 per cent were positive to a titer of 1–160. There is an obvious difference in the number of sera from pregnant women that

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TABLE I

Results of Weil-Felix reaction in sera from pregnant women

| | 1/20 DILUTION | | 1/40 DILUTION | | 1/80 DILUTION | | 1/160 DILUTION | |
|---|---|---|---|---|---|---|---|---|
| | No. pos. | Per cent pos. | No. pos. | Per cent pos. | No. pos. | Per cent pos. | No. pos. | Per cent pos. |
| Routine Wassermann Sera..... | 8 | 7.1 | 15 | 13.4 | 4 | 3.6 | 3 | 2.7 |
| Sera from Pregnant Women.... | 22 | 51.2 | 17 | 39.5 | 2 | 4.5 | 1 | 2.3 |

were positive to low titers from those of the routine Wassermann sera. The significance of these differences cannot be determined from the data available at present. A large number of sera and further work is necessary to evaluate these results.

*Conclusions.* There is a significant difference in the number of blood sera from pregnant women that give a low-titer-positive Weil-Felix test and the sera from men and non-pregnant women. Further work is necessary to evaluate the significance of this difference.

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# COMPLEMENT FIXATION IN TYPHUS FEVER

## A Preliminary Survey of Rats in Galveston, Texas

Weldon C. White*

The development of the complement fixation test for typhus fever during the last few years has furnished a very valuable tool for the study of the epidemiology of typhus fever and related diseases. During the past few months the author has begun a survey to determine the incidence of typhus fever in the rats of Galveston. To date, the sera of 29 rats, caught at random from several sections of the city, have been examined by both the complement fixation test by the method of Bengtson (Public Health Reports 59, 402–5 (1944) and the standard Weil-Felix test (Felix: Trans. Roy. Soc. Trop. Med. 37, 321–41, 1944). Of these 29 rats, 15 sera, or 51.79 per cent, were positive to a dilution of at least 1 to 10 by the complement fixation test and none were positive by the Weil-Felix test. In view of the increasing incidence of typhus in Galveston, this may prove of significance.

*From the Department of Preventive Medicine, Medical Branch, The University of Texas, Galveston. Received for publication May 1, 1945.

# QUANTITATIVE BACTERIOLOGIC ANALYSIS OF AIR IN CROWDED ROOMS

WELDON C. WHITE*

Since the development of the Wells air centrifuge for the bacteriologic analysis of air (Wells, 1933) there has been a great revival of interest in air-borne bacteria, and other infectious agents. Wells (1934) showed that the size of the droplets sprayed into the air determines the length of time they will remain suspended. The large droplets settle very quickly whereas the smaller ones dry rapidly and the nuclei remain suspended for long periods of time. Wells and Stone (1934) observed that certain bacteria (staphlococci, streptococci, and pneumococcus), whose natural habitat is the nasopharynx, survive long periods of time suspended in the air. Phelps and Buchbinder (1941) and Buchbinder et al. (1941), in extensive studies of streptococci suspended in the air, found that they not only remain suspended for long periods of time, but that they remain viable in the dust of the room for at least two weeks without impairment of virulence.

Numerous studies of the bacterial count of the air in various places have been made. Wells and Wells (1936), in a summary of their work, reported counts varying from 11 bacteria per 10 cubic feet in outside air in a quiet place to as high as 3,000 per 10 cubic feet, both in an experimental room where subjects were sneezing and in a textile mill where there was much dust. Buchbinder, Solowey and Solotorovitch (1938) studied conditions similar to these in New York City with comparable results. Lemon, Wise and Hamburger (1944) made bacterial counts in an army barracks and found that the total bacterial count depended upon whether the room was occupied or not and varied with the amount of activity therein.

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Experimental studies have shown that temperature and relative humidity play an important part in the survival of bacteria and viruses suspended in air. De Ome and the personnel of the U.S. Navy Medical Research Unit No. I (1944) found that the death rate of S. pulorum was in proportion to the temperature and to the relative humidity independent of the temperature. Williams and Gotaas (1942) also demonstrated that the death rate of air suspended organisms was dependent on relative humidity and increased as the humidity increased. The same has been shown to be true of viruses (Loosli, Lemon, Robertson and Appel, 1943).

Hart and his co-workers (1936, 1937, 1938, 1939, 1941) made extensive studies of the air in an operating room of a teaching institution simply by exposing Petri plates of blood agar. They discovered that the number of organisms settling out on the plates varied with the number of people in the room and the season of the year. The counts were higher in the winter when presumably the relative humidity was lowest and the ventilation poorest. They also noted that there was a high percentage of staphylococci present and concluded that the chief source of contamination was from the nasopharynx of the operators, since many of them carried these organisms in their nose and throat. MacDonald (1940), using the Wells air centrifuge, made a similar study of the operating and delivery rooms of another institution and obtained similar results. An average of the lowest counts was 71 bacteria per 10 cubic feet during the time the room was not in use and the highest single count was 678 per 10 cubic feet during a period of great activity. Streptococci and staphylococci were counted and found to parallel the total count but in much fewer numbers. He also found that ordinary blood agar plates exposed for fifteen minutes gave counts comparable to those of the Wells centrifuge.

Therefore, it may be assumed from the above experimental evidence that pathogenic organisms may remain suspended in the air for long periods of time and are at least potentially capable of causing infection. We may expect also that the degree of contamination of a given room will depend on its

size, the number of people present, the degree of activity, the length of time it is occupied, the temperature, the relative humidity of the atmosphere and indirectly the season of the year. The following experiments were undertaken to evaluate some of these factors with respect to local conditions as a possible basis for instituting some control over air contamination.

## Methods

A number of methods for determining the number of bacteria in the air quantitatively have ben devised (Wells, 1933; Bourdillion, Lidwell and Thomas, 1941; Moulton, Puck and Lemon, 1943; de Buy and Crisp, 1944). In the author's experiments, the Wells centrifuge was used in a few of the initial trials, but most of the work was done with a modification of the Hollaender and Dalla Valle funnel apparatus (Table I). This apparatus was observed to give somewhat

Table I

| Date | No. Bacteria / cu. ft. Wells centrifuge | No. Bacteria / cu. ft. funnel method | No. Bacteria settling in 15 min. on exposed plates |
|---|---|---|---|
| 12/29/44 | 6 | 5 | 11 |
| 1/ 8/44 | 5 | 6 | — |
| 1/ 9/44 | — | 8 | — |
| 1/22/44 | — | 19 | — |
| 2/ 5/44 | — | 15 | 24 |
| 3/ 8/44 | — | 15 | 24 |

Temperature—Maximum, 76°; Minimum, 73° F.
Relative Humidity—Maximum, 52%; Minimum, 50%.

higher counts under the same conditions; it was simpler to operate and the shorter sampling time was more convenient, especially in the operating room. The available vacuum line was found to be most satisfactory in the experimental surgery laboratory and in the operating room. In other places where no vacuum was available, a small vacuum pump designed for a dust impinger was used. The apparatus was calibrated by means of a mercury manometer so that one cubic foot per minute was pulled through the funnel. The size of the sample was varied by altering the sampling time. In all

experiments 10 per cent blood agar with Bacto blood agar base was used. In general, samples were taken every thirty minutes during periods of activity when greater variations in counts were expected and at longer intervals when there was no activity and less variation was expected. The sizes of the samples were from 1 to 5 cubic feet, depending on the expected count. On the whole, attempts were made to obtain from 30 to 100 colonies per plate. Blood agar plates also were exposed for fifteen minutes in the usual manner at irregular intervals for comparison purposes. Fifteen minutes was chosen as the amount of time for exposure because the average Petri plate has an area of one-fifteenth of a square foot and represents the number of organisms settling on one square foot in one minute. The plan of each experiment was to follow a day's activity in a given place. The relative humidity was determined by means of a sling psychrometer at least twice during each day's study.

## Results

The results of these experiments are given in the accompanying tables. Table I presents the results obtained in two laboratories (each about 30 by 45 by 10 feet) where there was practically no activity and only one or two people (controls) were present. These controls represent the counts to be expected in a quiet room with almost no contamination.

In Table II some data obtained in a lecture room are recorded. In an unoccupied room the count is very low (3 to

Table II

Lecture Room, 1/4/44, Funnel Method:

| Time | No. Bacteria per cu. ft. | Remarks |
|---|---|---|
| 12:20 | 3 | Room empty. |
| 12:30 | 5 | Room empty. |
| 2:00 | 34 | One-hour lecture just completed; approximately 100 persons present. |
| 4:00 | 36 | Two-hour lecture just completed; approximately 100 persons present. |
| 5:00 | 6 | Room empty; cross ventilation for one hour. |

Temperature: 12:15—74° F.
4:00—75° F.

Relative Humidity: 12:15—52%
4:00—52%

5 organisms per cubic foot). After a one hour lecture in a room in which there was practically no ventilation and in which approximately 100 people were present, the count rose to 32 organisms per cubic foot. After a two-hour lecture which immediately followed the first and under the same conditions, the count was practically the same. One hour after completion of the lectures, during which time the room was vacant and there was some cross ventilation, the count returned to the original level.

The results recorded in Tables III and IV were obtained in the hall of the Out-Patient Clinic which serves as a main

TABLE III

First Floor Hall at Out-Patient Clinic, 12/15/44, Wells Centrifuge:

| Time | No. of People Present | No. Bacteria per cu. ft. |
|---|---|---|
| 9:20 | 35 | 13 |
| 10:00 | 21 | 26 |
| 10:30 | 18 | 20 |
| 11:00 | 11 | 23 |
| 11:30 | 6 | 19 |
| 12:00 | 1 | 11 |
| 12:30 | 9 | 25 |
| 1:00 | 23 | 61 |
| 1:30 | 38 | 62 |
| 2:00 | 50 | 66 |

corridor of traffic through the building as well a waiting room for the patients of the medical and dermatology clinics in the mornings and the medical and pediatrics clinics in the afternoons. In general, the results parallel the number of people present. Some of the greater discrepancies between the Wells centrifuge and the funnel methods (Table IV) may be accounted for by the longer length of time of the runs necessary to obtain a satisfactory sample by the former method. The centrifuge was always run for ten minutes.

Tables V and VI show the data obtained in the experimental surgery laboratory during the class in dog surgery when 25 students were performing 5 to 6 operations simultaneously. Every one was required to don a cap and mask before entering the theater. In general, the activity was the

TABLE IV

| Time | No. of People Present | No. Bacteria per. cu. ft. Funnel Method | No. Bacteria per cu. ft. Wells Centrifuge | No. Bacteria per plate, exposed 15 minutes |
|---|---|---|---|---|
| First Floor Hall at Out-Patient Clinic, 1/8/45: | | | | |
| 9:05 | 35 | 34 | .. | .. |
| 9:30 | 35 | 24 | .. | .. |
| 10:00 | 35 | 61 | 10 | 49 |
| 10:30 | 13 | 32 | .. | .. |
| 11:00 | 5 | 15 | 6 | .. |
| 11:30 | 5 | 25 | .. | .. |
| 12:00 | 1 | 19 | 7 | 30 |
| 12:30 | 2 | 6 | .. | .. |
| 1:00 | 26 | 90 | 30 | .. |
| 1:30 | 25 | 10 | .. | .. |
| 2:00 | 25 | 30 | 14 | 76 |
| 2:30 | 15 | 26 | .. | .. |
| 3:00 | 10 | 27 | 12 | .. |
| 3:30 | 1 | 32 | .. | .. |
| 4:00 | 1 | 14 | 11 | 69 |
| 4:30 | 1 | 6 | .. | .. |
| 5:00 | 1 | 9 | 8 | .. |
| 12:00 | Temperature, 72° F.; Relative Humidity, 55%. | | | |
| 5:00 | Temperature, 72° F.; Relative Humidity, 65%. | | | |

TABLE V

| Time | No. of People Present | No. Bacteria per cu. ft. Funnel Method | No. Bacteria per plate Exposed 15 minutes | Remarks |
|---|---|---|---|---|
| Experimental Surgery Laboratory, Class in Dog Surgery, 1/22/45, Funnel Method: | | | | |
| 8:45 | 1 | 40 | .. | No activity. |
| 9:00 | 25 | 50 | 47 | Preparation for operations. |
| 9:30 | 25 | 18 | .. | Operations in progress. |
| 10:00 | 25 | 19 | .. | Operation in progress. |
| 10:30 | 25 | 11 | .. | Operation in progress. |
| 11:00 | 25 | 10 | .. | Operation in progress. |
| 11:30 | 25 | 12 | .. | Operation in progress. |
| 12:00 | 16 | 24 | .. | Some operations completed. |
| 12:30 | 2 | 30 | 59 | All operations completed (cleaning in progress). |
| 1:00 | 1 | 34 | .. | Cleaning in progress. |
| 2:30 | 1 | 6 | .. | No activity. |
| 4:00 | 1 | 10 | 16 | No activity. |

| *Time* | *Temperature* | *Relative Humidity* |
|---|---|---|
| 9:00 | 71° F. | 50% |
| 12:30 | 74° F. | 40% |
| 4:00 | 74° F. | 40% |

TABLE VI

Experimental Surgery Laboratory, Class in Dog Surgery, 2/5/45:

| Time | No. of People Present | No. Bacteria per cu. ft. Funnel Method | No. Bacteria per plate. Exposed 15 minutes | Activity |
|---|---|---|---|---|
| 9:15 | 25 | 58 | 68 | Preparation for operations. |
| 10:00 | 25 | 23 | .. | All operations in progress. |
| 10:30 | 25 | 14 | .. | All operations in progress. |
| 11:00 | 25 | 18 | .. | All operations in progress. |
| 11:30 | 25 | 9 | .. | All operations in progress. |
| 12:00 | 20 | 31 | .. | Two operations completed. |
| 12:30 | 9 | 19 | .. | All but one operation completed. |
| 1:00 | 1 | 39 | .. | All operations completed. |
| 1:30 | 2 | 47 | .. | Cleaning in progress. |
| 3:00 | 1 | 20 | 19 | No activity. |
| 4:30 | 1 | 13 | .. | No activity. |

| *Time* | *Temperature* | *Relative Humidity* |
|---|---|---|
| 9:30 | 74.5° F. | 50% |
| 3:00 | 75.5° F. | 40% |

same as in a general operating room, except on a larger scale and in a comparatively much larger room. The bacterial counts were highest during the preparatory period when the laboratory helper was setting up the tables and the students were coming in and preparing for the operations. After the operations had begun and the activity was much less, there was a drop in the count. Following the completion of the operations, when activity increased and during the cleaning of the room, the count rose again. Later in the day, after cessation of all activity, the count fell to the level of any ordinary quiet room.

Tables VII and through XI give data obtained in a general surgery operating room of a teaching hospital. The results are similar to those obtained for the experimental surgery laboratory. The counts were observed to be somewhat higher, which can be accredited to the fact that the room was much smaller and much more crowded. In other words, there was much less space per person in the operating room than in the experimental surgery laboratory. The effect of activity on the bacterial count is fairly well shown in all of the tables. Peak

TABLE VII

Operating Room, Room No. 1, Clinic Surgery, 1/12/45:

| Time | No. of People Present | No. Bacteria per cu. ft. Funnel Method | Remarks |
|---|---|---|---|
| 7:45 | 4 | 49 | Preparation for operation. |
| 8:00 | 6 | 30 | Patient brought in. |
| 8:30 | 9 | 22 | Operation started. |
| 9:00 | 10 | 7 | Operation in progress. |
| 9:30 | 10 | 16 | Operation in progress. |
| 10:00 | 8 | 15 | Operation completed. |
| 10:30 | 8 | 36 | New patient in at 10:15. |
| 11:00 | 12 | 25 | Operation started. |
| 11:30 | 11 | 34 | Operation in progress. |
| 12:00 | 9 | 19 | Operation in progress. |

| *Time* | *Temperature* | *Relative Humidity* |
|---|---|---|
| 8:00 | 76.0° F. | 56% |
| 11:30 | 79.5° F. | 68% |

TABLE VIII

Operating Room, Room No. 1, Clinic Surgery, 1/14/45, Funnel Method:

| Time | No. of People Present | No. of Bacteria / cu. ft. | Estimated No. of Staphylococci / cu. ft. | No. of Bacteria / Exposed Plate | Estimated Staphylococci / Plate | Remarks |
|---|---|---|---|---|---|---|
| 8:10 | 8 | 98 | 45 | 66 | 33 | Preparation of patient. |
| 8:30 | 10 | 30 | 28 | .. | .. | Operation in progress. |
| 9:00 | 6 | 51 | 25 | .. | .. | Operation completed. |
| 9:30 | 13 | 53 | 36 | 51 | 35 | Preparation of patient. |
| 10:00 | 13 | 34 | 30 | .. | .. | Operation in progress. |
| 10:30 | 13 | 68 | 41 | 35 | 26 | Operation in progress. |
| 11:00 | 13 | 35 | 15 | .. | .. | Operation in progress. |
| 11:30 | 9 | 63 | 13 | .. | .. | Operation completed. |
| 12:00 | 1 | 65 | 23 | .. | .. | Patient out at 11:40. No activity. |
| 12:30 | 4 | 68 | 32 | .. | .. | Cleaning in progress. |
| 1:00 | 3 | 54 | 30 | 25 | 10 | Very little activity. |
| 2:00 | 1 | 46 | 33 | .. | .. | No activity. |
| 3:00 | 1 | 37 | 33 | .. | .. | No activity. |
| 4:00 | 1 | 40 | 29 | 17 | 4 | No activity. |

| *Time* | *Temperature* | *Relative Humidity* |
|---|---|---|
| 8:20 | 82° F. | 40% |
| 11:50 | 81° F. | 32% |

TABLE IX

Operating Room, Room No. 1, Clinic Surgery, 1/25/45–1/26/45, Funnel Method:

| Time | No. of People Present | No. of Bacteria / cu. ft. Estimated | No. of Staphylococci / cu ft. | No. of Bacteria / Exposed Plate | Estimated Staphylococci Plate | Activity |
|---|---|---|---|---|---|---|
| 5:15 P.M. | 1 | 8 | 2 | .. | .. | No activity. |
| 9:00 P.M. | 1 | 13 | 3 | 19 | 14 | No activity. |
| 6:45 A.M. | 2 | 22 | 16 | 10 | 14 | No activity. |
| 7:30 A.M. | 5 | 37 | 16 | .. | .. | Preparation for opreation. |
| 8:00 A.M. | 7 | 34 | 17 | .. | .. | Patient brought in. |
| 8:30 A.M. | 9 | 37 | 6 | 35 | 21 | Operation in progress. |
| 9:00 A.M. | 8 | 42 | 15 | .. | .. | Operation in progress. |
| 9:30 A.M. | 8 | 41 | 14 | .. | .. | Operation in progress. |
| 10:10 A.M. | 9 | 95 | 30 | .. | .. | Operation completed, patient out of room. |
| 10:45 A.M. | 14 | 56 | 20 | .. | .. | Operation started. |
| 11:30 A.M. | 12 | 43 | 20 | .. | .. | Preparation of new patient. |
| 12:00 NOON | 11 | 38 | 21 | .. | .. | Operation in progress. |
| 12:45 P.M. | 10 | 29 | 12 | .. | .. | Operation in progress. |
| 2:20 P.M. | 3 | 34 | 12 | .. | .. | Preparation for emergency operation. |
| 4:30 P.M. | 7 | 48 | 13 | .. | .. | Operation completed. |
| 5:30 P.M. | 2 | 31 | 10 | 33 | 28 | No activity. |
| 7:45 P.M. | 1 | 24 | 10 | 25 | 20 | No activity. |

| *Date* | *Temperature* | *Relative Humidity* |
|---|---|---|
| 1/25/45 | 77° F. | 32% |
| 1/26/45 | 79° F. | 42% |

activity occurred at the beginning of the day during the period of preparation when several people were constantly moving about in the room while others were entering and leaving it; then again, at the completion of one operation and the beginning of another when one patient was removed from the room and another brought in, necessitating great activity and the opening and closing of the doors in the room.

One point of interest noted on all the plates exposed in the operating room, whether simple exposure or in the funnel

TABLE X

Operating Room, Room No. 1, Clinic Surgery, 2/2/45:

| Time | No. of People Present | No. of Bacteria / cu. ft. Funnel Method | No. of Bacteria / Exposed Plate | Activity |
|---|---|---|---|---|
| 6:45 | 1 | 6 | 8 | None. |
| 7:30 | 5 | 26 | .. | Preparation for operation. |
| 8:00 | 5 | 19 | .. | Preparation for operation. |
| 9:00 | 12 | 42 | .. | Preparation of patient. |
| 9:30 | 12 | 10 | .. | Operation in progress. |
| 10:00 | 14 | 23 | 20 | Operation in progress. |
| 10:30 | 13 | 19 | .. | Operation in progress. |
| 11:10 | 8 | 26 | .. | Patient out and new patient in. |
| 11:30 | 14 | 26 | .. | Operation in progress. |
| 12:00 | 10 | 11 | .. | Operation in progress. |
| 12:30 | 8 | 12 | .. | Operation in progress. |
| 1:00 | 3 | 15 | 26 | Operations completed, no activity. |
| 1:30 | 8 | 29 | .. | Operation started. |
| 2:00 | 8 | 18 | .. | Operation in progress. |
| 2:30 | 8 | 12 | .. | Operation in progress. |
| 3:00 | 4 | 15 | 31 | Operation completed, patient out. |
| 3:30 | 4 | 11 | .. | Cleaning finished. |
| 4:00 | 1 | 4 | .. | No activity. |
| 5:00 | 1 | 9 | .. | No activity. |
| 6:00 | 1 | 5 | .. | No activity. |
| 9:00 | 1 | 7 | .. | No activity. |
| 12:00 | 1 | 2 | 10 | No activity. |

| *Time* | *Temperature* | *Relative Humidity* |
|---|---|---|
| 6:45 A.M. | 72° F. | 56% |
| 3:00 P.M. | 75° F. | 46% |

apparatus, was a predominance of one type of colony. This was not true of any other place where plates were exposed. These predominating colonies proved to be staphylococci by gram stain. They were all of the non-pigmented variety, with one or two exceptions, and some were hemolytic. The number of staphylococci per cubic foot was estimated in two experiments by counting all colonies similar to those found to be staphylococci by gram stain. These data are recorded in Tables IX and X. The numbers per cubic foot parallel the total bacterial count.

In both the operating room and the experimental surgery laboratory all of the occupants wore caps and masks covering the mouth and nose at all times throughout the procedure. Much may be found in the literature about the efficiency of

TABLE XI

Operating Room, Room No. 1, Clinic Surgery, 3/9/45:

| Time | No. of People Present | No. of Bacteria / cu. ft. Funnel Method | No. of Bacteria / Exposed Plate | Activity |
|---|---|---|---|---|
| 8:30 | 5 | 21 | 19 | Waiting for patient. |
| 9:00 | 10 | 17 | .. | Patient in at 8:50. |
| 9:30 | 12 | 16 | .. | Operation in progress. |
| 10:10 | 10 | 19 | .. | Operation in progress. |
| 10:45 | 10 | 19 | .. | Operation in progress. |
| 11:30 | 9 | 25 | 15 | Operation in progress. |
| 1:00 | 1 | 29 | .. | Operation completed. |
| 4:30 | 1 | 17 | 12 | No activity. |

| *Time* | *Temperature* | *Relative Humidity* |
|---|---|---|
| 8:30 | 74° F. | 50% |
| 4:30 | 69° F. | 50% |

face masks (Walker, 1930; Blatt and Dale, 1933; Davis, 1937; Gauthie, 1937, and Rooks, Crally and Barns, 1941). Most masks have been proved to be very poor filters; they remove only a small part of the number of organisms sprayed into the air and the most efficient ones thus far tested remove approximately 97 to 98 per cent of the organisms. However, the more efficient the mask may be as a filter, the more resistant it will be to the transmission of air, and as a consequence the organisms will be sprayed out around the sides of the mask. Thus, in any operating room, much of the contamination may come directly from the occupants of the room in spite of their masks.

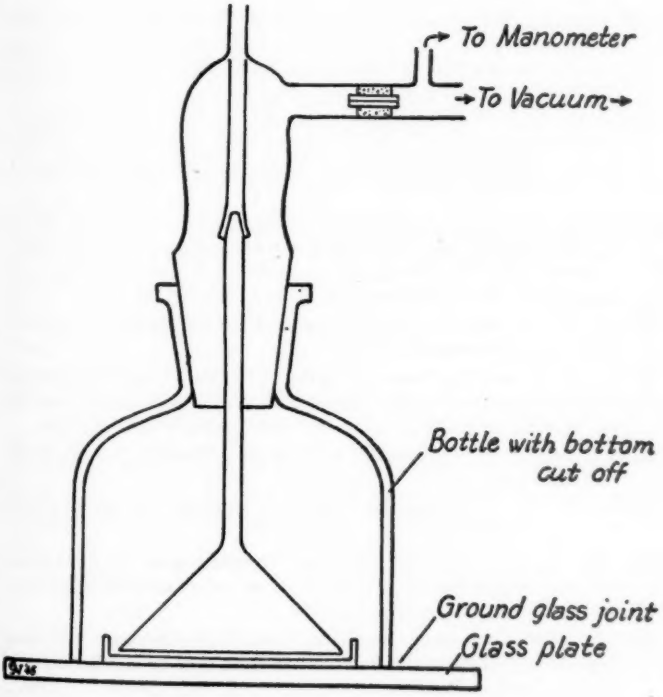
The dust arising as a result of the activity in the room is an additional source of contamination. The floors and other surfaces, as well as the sheets and blankets brought in with the patient, all contribute to this type of contamination. Whether it is the dust or the contamination from the nasopharynx of the operators that is most important cannot be determined from these data. Hart and Schiebel (1939) believed that the nose and throats of the operators was the most important consideration.

The relative range of humidity in these experiments was from 32 per cent to 68 per cent and the temperature from 71 F. to 79.5 F. During January and February, when most of

this data was collected, the lowest outside temperature recorded by the local weather bureau was 40 F. and the highest was 71 F., with a mean of 54.6 F. for January and 59 degrees for February. The lowest mean relative humidity for any one day was 72 per cent and the highest was 92 per cent. Thus, the inside relative range in humidity was higher than would be found in a colder and dryer climate. As can be seen in Tables IX and X, the bacterial counts were highest and tended to persist longer when the relative humidity was lowest.

## Summary and Conclusions

Quantitative bacterial counts were made in an operating room, an experimental surgery laboratory where a class in



dog surgery was in progress, a hall and waiting room of an Out-Patient Clinic and a lecture room. The bacterial counts were found to vary with the size of the room, the number of people present, their activity and the relative humidity of the atmosphere.

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# PHARMACOLOGICALLY ACTIVE AGENTS FROM THE SEA*

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Although many competent medical workers have contributed to marine biology, its medical aspects have not received the same systematic attention which has resulted in major advances along the lines of taxonomy, embryology and general physiology. Contributions of medical interest in marine biology are widely scattered in the literature; over 180 journals supplied the source material for this relatively casual review of a single, closely defined phase of this field. To our knowledge, there is no recent review of pharmacologic agents obtained from the sea. The present review in the main covers developments over the past twenty years; it makes no pretense of being complete, since many significant findings are hidden in the literature through publication as findings incidental to studies in general physiology. It is designed as an introduction to the field and not as an exhaustive compilation; difficulties of attaining any degree of thoroughness would render further lucubration unprofitable. Much of the literature cited has been seen by us only as abstracts, since the special journals chosen by many workers are not commonly available. Selection of material has been restricted to illustrative examples of the diverse types of agents from marine sources, and omissions have been purposeful in the interest of brevity.

A considerable body of knowledge has become available in regard to poisonous marine organisms, due in large part to their clinical importance. For expediency, this material is presented as a separate report by one of us *(305)*.

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*From the Department of Pharmacology, The University of Texas Medical Branch, Galveston. Received for publication May 10, 1945. N. B. The large bibliography of this unusual review suggested the wisdom of using numerical text references. The bibliography, however, is arranged in numerical sequence, alphabetically, according to author. Titles are omitted to save space.

## Historical Aspects

Medical uses of marine products in Chinese and Indian medicine are omitted from consideration because of the mass of uncritical material. In antiquity, marine forms were apparently not in common use except as food. Scribonius Largus suggested the therapy of headache with *Torpedo*, ca. 47 A. D. In the first of *The Seven Books of Paulus Aegineta (11a)*, nutritional values and laxative and antidiarrheic actions of various marine organisms are noted. Adams' commentaries *(11a)* include an account of beliefs regarding exclusively ichthyophagous peoples, who are reputed to have been free from disease but short-lived. In addition to his extensive discussion of dietary values, Adams' commentaries record that various fish "engender phlegm," that sea urchins are diuretic, that mollusks are aphrodisiac, that excessive eating of elasmobranch flesh "blunts the sight" and that pickled fishes are stomachics.

"Living creatures" mentioned in the second of the five books of Dioscorides *(87a)* include many from the sea. *Echinus esculentus* is recommended for abdominal and urinary complaints; roasted or burnt, it is used against dermatitides, in cleansing foul ulcers and for repressing "excrescencies of ye flesh." Burnt *Murex brandaris* dries and cleans the teeth, represses excrescent flesh and draws and heals boils; preparations of the whelk, *Buccinum*, and "Pontick mytuli" act similarly. The columellae of mollusks, burnt, have a like effect but are somewhat more caustic. Ashes of marine crabs are said to be less effective than those of river crabs against the bite of mad dogs, chapped skin, chilblains and cancer. *Scorpaena scrofa* is used in eye diseases. *Trachinus draco*, opened and applied to the wound, is recommended for *T.* stings, as is also *Mullus barbatus;* the latter is useful against scorpion stings and spider bites as well. Any of the polychaet worms "sod in oil" and anointed "doth get off the haire." The sea-hare, *Aplysia depilans*, and sea-nettles are also depilatories, while ashes of the sea-horse cure alopecia. *Torpedo*, when applied "in griefs of long continuance about ye head, doth assuage the fierceness of

the grief" and also "doth stay up the seate." The sting-ray is held useful in toothache; an application of the barb to a "pained tooth" . . . "breaks and casteth him out." Several uses are presented for *Sepia*, chiefly in eye diseases. Soups of fishes and bivalves are employed for their effects on the stomach. Beliefs as to the medicinal virtues of a number of common marine teleosts also are noted. Application of a paste of fresh jellyfish is said to relieve gout and chilblains.

*Recent.*—More recent historical material on medicinal uses of marine products is available in Garzon Maceda's *Zoo-Farmacia (113)* which follows Dioscorides *(87a)* closely but with a few additions. This book deals systematically with sponges, noting their surgical use and I content; actinia, from which the nematocysts are used as rubefacients or vesicants; medusae, similarly used in rheumatism and neuralgia; coral, in powder, as an antacid, a dentifrice and a remedy for diarrhea and internal hemorrhage, and *Sepia* bone, also used as a dentifrice. Oysters are discussed in detail. Collection is said to be forbidden in France from June 15 to September 1, since at this time the oysters may contain a toxic principle, mytilotoxin. Use of oysters as a medicinal food is related to their easy digestibility, but their value is questioned by the statement that 16 dozen are needed to satisfy the daily N requirement. Pearls have been used to control tremors and heart disease, internal hemorrhage and bulimia, and as a tonic, antacid or astringent.

In discussion of fish used medicinally *(113)*, the same indications noted by Dioscorides *(87a)* are given for *Hippocampus antiquorum; Scorpaena; Torpedo; Trachinus draco;* and ashes of the head of *Smaris*. Eating of *Mullus barbatus* is said to increase visual acuity, whereas Dioscorides holds that it may "cause dullness of sight." Uses of fish oils before 1915 are briefly considered.

Youngken *(354)* presents a thorough discussion of characteristics and uses of *Fucus, Ascophyllum, Chondrus, Gigartina* and *Gelidium* species.

Table 1 presents the sources and actions of a group of substances of marine origin found in the *American Dispensatory* of 1814 *(77)* and the *U. S. Dispensatories* of 1858 *(348)* and

TABLE I

*Older Marine Drugs*

| Drug | Source | Action | Ref. |
|---|---|---|---|
| Bromine and derivatives | Sea water | Caustic; antiseptic; hypnotic | ... |
| Magnesium and derivatives | Sea water | Antacid; cathartic; narcotic | ... |
| Agar-agar | Algae *(Fucus; Gelidium; Gracilaria)* | Demulcent; colloid laxative | 348 |
| Algin | Algae *(Fucus)* | Demulcent | 349 |
| Celon moss | Algae *(Gigartina lichenoides)* | Demulcent | 77 |
| Helminthocorton | Algae *(Fucus helminthocorton)* | Anthelminthic | 348 |
| Iodine and derivatives | Algae *(Ecklonia; Sargassum; Fucus)* | Antiseptics; expectorant; antiluetic | 349 |
| Irish moss | Algae *(Chondrus crispus)* | Demulcent | 348 |
| Yellow bladderwrack | Algae *(Fucus)* | Antacid | 77 |
| Ambergris | *Physeter macrocephalus* | Stimulant | 348 |
| Cod liver oil | *Gadus morrhua; G.* spp. | Source of vitamins A and D | 77 |
| Crab claws | *Cancer pagurus* | Antacid | 77 |
| Crab stones | *Cancer* spp. | Antacid | 77 |
| Coral, red | *Gorgonacea* spp. | Antacid | 77 |
| Cuttlefish bone | *Sepia officinalis* | Antacid | 348 |
| Halibut liver oil | *Hippoglossus hyppoglossus* | Source of Vitamins A and D | 349 |
| Isinglass | *Gadus merluccius; Otolithus regalis; Acipenser* spp. | Demulcent | 77 |
| Oyster | *Ostrea edulis* | Medicinal food | 77 |
| Oyster shell | *Ostrea edulis* | Antacid | 77 |
| Shark liver oil | *Squalus* spp. | Source of vitamins A and D | ... |
| Spermaceti | *Physeter macrocephalus* | Emollient | 77 |
| Sponge, burnt | *Spongia officinalis* | Thyroid stimulant | 77 |
| Turtle oil | *Chelonia* spp. | Cosmetic | 349 |

1937 *(349)*. The single substance from the sea of greatest economic and biologic importance is undoubtedly NaCl. The remainder of the agents tabulated, with the exception of the fish oils, agar, and the elements or their derivatives, are not of any great consequence in modern medicine, but persist as illustrations of the wide variety of marine drugs found empirically.

A list of sources of animal drugs, including a number of marine forms, is given in Coxe's *American Dispensatory* of 1814 *(77)*. This list is reproduced below.

*List of Animals which furnish Articles of* ***Materia Medica,*** *arranged according to Cuvier's System*

| | |
|---|---|
| | MAMMALIA. |
| RODENTIA. | Castor fiber. |
| PACHYDERMATA. | Sus scrofa. |
| RUMINANTIA. | Moschus moschiferus. |
| | Cervus elaphus. |
| | Ovis aries. |
| | Bos taurus. |
| CETACEA. | Physeter macrocephalus. |
| | AVES. |
| GALLINÆ. | Phasianus gallus. |
| ANSERES. | Anas anser. |
| | PISCES. |
| CHONDROPTERYGII. | Acipenser sturio, stellatus, huso, ruthenus. |
| | CRUSTACEA. |
| CANCERES. | Cancer pagurus, astacus. |
| | INSECTA. |
| COLEOPTERA. | Lytta vesicatoria. *(Meloe vesicatorius.)* |
| | Meloe proscarabæus. |
| HYMENOPTERA. | Cyneps querci folii. |
| | Apis mellifera. |
| | Formica rufa. |
| HEMIPTERA. | Coccus cacti. |
| GNATHAPTERA. | Oniscus asellus. |
| | MOLUSCA. |
| CEPHALOPODA. | Sepia officinalis. |
| ACEPHALA. | Ostrea edulis. |
| | VERMES. |
| | Hirudo medicinalis. |
| | ZOOPHYTA. |
| CERATOPHYTA. | Gorgonia nobilis. *(Isis nobilis.)* |
| SPONGIA. | Spongia officinalis. |

## Sea Water

Studies with sea water include its therapeutic effects, use as a physiologic solution for surviving tissues, effects on parenteral administration in animals and on ingestion or prolonged contact in man, and its growth-promoting and inhibiting effects on microorganisms. Interpretations must take into account the consideration that sea water is variable in content of its several constituents; many data are available on this point, particularly in recent issues of the *Journal of Marine Research*. The salt content of sea water varies roughly between 2–4% *(287)*.

*Therapy.*—Under the direction of the Committee on American Health Resorts of the American Medical Association, an authoritative appraisal *(287)* was made recently of the rationale of thalassotherapy. Most of the factors concerned in the beneficial actions of sun, air and water are purely physical, but demonstration of appreciable amounts of I in the air at the seashore affords a point of pharmacologic interest.

The remarkable claim is made *(322)* that injection of sea water intravenously or intraperitoneally in dogs effects a complete cure of sarcoptic or follicular mange. Ringworm in a bull also was successfully treated by repeated intravenous injections.

*Use as a physiologic solution.*—Diluted, isotonic sea water is recommended *(177)* as a suitable menstruum for survival of frog tissues; it is improved by addition of 1:10000 lecithin. Isotonic sea water maintains mammalian smooth muscle well, but is not adequate for mammalian hearts *(355)*. For marine forms, natural sea water controls arrhythmias and strengthens teleost or selachian hearts, while artificial sea water fails in this action *(207)*. A great deal of work has been done with marine and freshwater forms, including algae, various eggs and fish, dealing with reactions and adaptations to diluted sea water; in the main, these reactions do not immediately involve chemical aspects of pharmacology and so are omitted from this review.

*Parenteral effects.*—Toxic actions of sea water on rapid intravenous administration to guinea pigs are considered *(259)* chiefly due to Mg narcosis. The lethal dose in mammals depends on rate of injection *(258)*. Effects upon renal excretion,

and the toxicity, have been extensively studied in rabbits *(260)*. Intravenous doses up to 30 ml/kg. have no effect on blood sugar, but increase the respiratory exchange and the respiratory quotient *(256, 257)*. An increased O exchange in the lungs is also claimed *(324)*. Repeated injections influence body weight and blood picture of guinea pigs *(176)*; effects on the histology of the vagina of spayed mice have also been studied *(167)*. Depression of the sympathetic nervous system may occur with large doses, but no side-effects are noted when up to 40 ml/kg. of isotonic sea water replace blood in mammals *(355)*.

*Effects on man.*—Renewed interest in effects of ingestion of sea water is inspired by the war; several reports have appeared recently utilizing modern techniques. In amounts up to 400 ml. daily, ingestion of sea water may increase body water in the "man on a raft" *(175)*. Larger amounts, by mouth or rectum, are harmful. The naval surgeon, Gauthier, first invented an apparatus for distillation of sea water in 1717. A modern approach *(297)* to the problem of removal of salts from sea water involves a simple double adsorption technique which reduces the salt content to 0.58%.

Topical effects of sea water are important in regard to salt-water rash and immersion foot *(120)*; but the etiology of these conditions involves physical rather than chemical factors. Sea water is classed as a cancer-provocative agent of significance in skin cancer among Navy personnel *(244)*; it is not considered carcinogenic in the sense that it will cause cancer directly, but only in that it will induce cancer to develop at the site of irritation. Inasmuch as skin cancer is treated easily in comparison with deeply seated tumors, it is believed that this cancer-provocative action of sea water has a certain prophylactic value.

*Growth substances.*—Growth-promoting properties of sea water for the diatoms *Nitzschia closterium* and *Skeletonema costatum* differ according to the locality and depth from which it is obtained, and are unrelated to variations in mineral constituents *(197)*. Bioassay of growth substances by effects on plankton is a better criterion of the content than are chemical analyses for N and P *(280)*.

*Bacteriostatic actions.*—Fresh sea water ordinarily contains few bacteria; on use for bathing, the count increases and then decreases after further use, despite lack of any demonstrable bacteriophage *(81)*. Many freshwater bacteria will survive for long periods and adapt to sea water *(59)*; *Eberthella typhosa* and *Escherichia coli* may survive for ten months in polluted sea water *(32)* and *Vibrio cholerae* survives for a long time also *(353)*. There is no reason to believe that significant bacteriostatic mechanisms other than dilution commonly operate to sterilize sea water, although Waksman *(337)* notes that viability is affected by plankton. Even water of the Great Salt Lake contains bacteria adapted to its high salinity, although it is lethal to *Esch. coli*, staphylococci and marine bacteria *(356)*.

Prevalence of ascariasis in Samoa is said *(346)* to be due in part to the use of polluted sea water as a seasoning, in place of salt; *Ascaris* eggs mature well in sea water.

## Algae

Alginic acid or algin has been used commercially as a substitute for gum arabic and tragacanth; it has many possibilities of further application if its use becomes feasible economically *(86, 217)*. Its extraction from *Laminaria* is described by Dillon *(87)*. Fe alginate, algiron, has been used in therapy of anemia *(206)*. Metabolic studies of algin itself have been made *(227)*.

American sources of agar have been exploited during the war, notably in Florida and California. *Gracilaria confervoides* of the N. Carolina coast yields an agar different in some respects from *Gelidium* agar *(151)*. New Zealand *Gigartina decipiens* serves as a substitute for Irish moss *(17)*. Interest in economic uses of algae includes Russian studies of production of alcohol by fermentation of *Laminaria (58)*; quantities of acetone were prepared by fermentation of algae on our West Coast during the First World War *(217)*.

Reid Hunt *(152)* in 1910 demonstrated that the I of bladderwrack, *Fucus vesiculosus*, has 80 to 200 times the thyreotropic activity of other organic or inorganic I compounds except thyroid I itself, which is some 50 times more active. This study,

as well as investigation of I compounds of thyroid and ovaries of marine forms (*v.* under Hormones), could well be repeated by modern techniques. Hunt employed the acetonitrile test for thyreotropic activity.

Marine algae contain growth hormones *(318)*. Similar auxins are found in the diatoms *Phyllospadix* and *Zostera (319)*. The diffusion constant of auxins from algae indicates that these are mainly indoleacetic acid *(320)*.

The use of helminthocorton in European folk-medicine years ago *(348)* is recalled by the description of an ascaricide from *Sargassum thunbergii (119)* and a report that horses fed seaweed in amounts replacing 20% of oats in the diet show fewer strongyle and ascarid ova in their feces than do controls *(212)*.

Moore *(217)* and Dillon *(86)* review the chemical products of marine algae. Other references are made to various constituents of algae in the present review under the different classes of active agents described below.

## Inorganic Substances in Marine Life

Interest in inorganic substances in marine forms has centered chiefly in I and As. Numerous studies have dealt with extensive investigations of groups of elements in different marine organisms *(67, 228, 331)* with reference to environment or other factors. Reports on occurrence of heavy metals and other elements appear sporadically.

*Iodine.*—Closs *(72)*, in an exhaustive monograph, reported the occurrence of I in sea water, algae, various invertebrates and fish. The I of *Laminaria digitata* is chiefly iodide. In the crustacea *Homarus vulgaris* and *Pandalus borealis*, I is mainly in the shell and ovary. Tissue distribution in fish is also reported.

The I content of 14 marine algae is reported from China *(306)*. In spongin, both diiodotyrosine and dibromotyrosine are found as well as I *(7)*. The I content of different marine crustacea and its distribution in their tissues have been studied *(273)*. In an interesting ecologic note, Lunde *(188)* reports that the I content of fish, starfish and shellfish at Woods Hole is

generally less than in Norwegian forms. I compounds resembling thyroxine have been found in *Fucus vesiculosus (152)* and in testes and ovaries of *Echinus esculentus (68)*, as noted elsewhere in this review.

A number of workers have stressed the importance of marine foods as a source of I. In general diets, I is highest in edible seaweeds and marine fish *(139)*. Fishmeal is a rich source of I *(277)*. The significance of marine fish in the diet in preventing thyroid disease is recognized *(101)* and greater use of marine foods is urged in certain localities such as Latvia *(173)* for this reason. The possibility of indirect use of marine I is suggested by the finding *(30)* that seaweed fed to cows increases the I content of milk; when seaweed is fed to chickens, the I content of the eggs is increased.

*Arsenic.*—Marine fish contain more As than do fresh-water fish *(96)*, presumably due to the high As content of planktonic crustacea on which they feed. The As content of sea water is variable, with a seasonal change due to growth of algae *(21)*. As is present in fish oils and eels as well as fish *(270)*. The amounts involved would not appear to be dangerous at any reasonable level of intake, although some lots of New Zealand *Gigartina decipiens* may require dilution with As-low Irish moss to meet standards for this material *(17)*.

*Other elements; heavy metals.*—Two reports on the I, As, Fe, Ca and S content of Chinese medicinal algae *(261)* and the Na, K, Ca, Fe and Cu content of 16 marine gastropods *(201)* are representative of work in this field. An extraordinarily high Mg content is found in the periwinkle *Littorina littorea* and the whelk *Buccinum undatum (202)*. Ca metabolism in mollusks, and the role of carbonic anhydrase, have been intensively studied; the findings here are beyond the scope of this review.

Cu compounds are primarily of interest in O transport and tissue respiratory enzymes in marine invertebrates, but other marine forms are relatively good sources of Cu. The Cu content of Bengal fish *(272)* and of lamellibranchiate mollusks *(242)* is known; values are also given for Co and Zn in mollusks *(242)*. Ni is found in mollusks and is particularly high in *Cardium edule*, in which form tissue distribution of Ni has been studied

*(241)*. The Ti content of various fish and shellfish has been noted *(41)*, and V has been studied in *Phalluris obliqua, Ciona intestinalis (330)* and other ascidians. Fish are deficient in Mn, in comparison with other foods *(184)*.

## Marine Products as Medicinal Foods and Experimental Nutrients

Apart from their value as a source of I, vitamins *(q.v.)* and trace elements in the diet, marine forms have a certain standing as medicinal foods. Many reports are available on the protein, carbohydrate and fat in marine organisms and the adequacy of these components in animal nutrition; these studies are not reviewed here. A few examples having some pharmacologic interest may be mentioned.

The present status of the oyster as a medicinal food has recently been reviewed *(109)*, with special reference to an antianemic principle; analyses are given in detail, and are also noted elsewhere *(137)*. Marine algae have been proposed as an important source of food *(69)*. Plankton *(133)*, and especially zooplankton *(347)*, are extolled for this purpose. The fats of marine crustacea in plankton are identical with fats of fish feeding upon them *(186)*; fish probably deposit their food fat unchanged. A brief general survey of the food value of marine products is available *(104)*.

Fish meal is widely used in animal rations and has been extensively studied. Dehydrated starfish meal *(Asterias forbesi)* is a satisfactory protein source for chick starter rations *(219)*. A specially prepared fish meal is an adequate protein source in a vitamin A-low diet for rats *(198)*.

Enrichment of media for fastidious pathogenic bacteria with 5% fishroe infusion or 20% quahaug infusion has certain advantages over other types of enrichment *(155)*.

*Athiaminosis from feeding raw fish.*—A paralysis resembling Wernicke's syndrome *(12)* is produced in foxes fed raw fish, either fresh or frozen. This is known as Chastek paralysis and is recognized to be an athiaminosis *(125–127, 142, 171, 233)*. It occurs mainly in foxes fed carp, but is caused by raw smelt

as well *(142)*; cats fed raw herring develop a similar syndrome *(298)*. The antithiamine factor is an enzyme *(298)*. It occurs mainly in the viscera, with little in the muscle tissue of carp *(281)*. Deutsch *(84)* finds that the degradation of thiamine by raw smelt leaves no thiazole or pyrimidine remainder, but raw carp has been shown *(171)* to contain 2 thiamine-destroying fractions which act, when combined, to produce 4-methyl-5-hydroxyethylthiazole and 2-methyl-4-amino-5-hydroxymethylpyrimidine from thiamine. Chastek paralysis is not cured by other members of the B complex than thiamine itself *(142)*. It may be avoided by intermittent rather than continual use of raw fish in the diet.

## Vitamins

Sollmann *(294)* presents a brief historical review of medical uses of the fish oils. These agents are important as a commercial source of vitamins A and D, and their study has increased knowledge of metabolism of these vitamins. The industrial aspects of codliver oil production in Iceland *(307)* and shark liver oil production on the West Coast *(304)* have been reviewed. Data on constitution of fish oils are available from many sources, and also have been reviewed *(231, 232)*. There are numerous reports of the vitamin A and D content of individual marine forms; studies of the distribution of these 2 vitamins in oils of different organs of the shad *Alosa sapidissima* and the mackerel *Scomber scombrus (254)*, of their occurrence in canned shrimp *(218)* and in *Thunnus thynnus* and *Sarda sarda (83)*, and of their presence in oysters and resistance to cooking *(344)* are representative of the diverse types of research in this field. Hopkins *(146)* recommended the use of marine invertebrates common in Texas waters as sources of vitamins A and D, since quantities of fish oils are imported.

Less is known of the occurrence of water-soluble vitamins in marine forms. The vitamins are discussed individually below.

*Vitamin A.*—The vitamin A content of the flesh *(196)* and liver oils *(140)* of a number of fish has been determined. In

the same species, older fish usually contain more vitamin A than younger fish *(140)*. Vitamin A has been found in the eels *Anguilla vulgaris* and *A. aucklandii (94)* and in liver oils of the corvina *Micropogon* and the pescadillo *Cynoscion (121)*; but it is apparently absent from the liver oil of the seal *Callorhynchus (121)*. It is claimed that the sterol fraction of cod and other fish liver oils gains vitamin A activity on irradiation and gives the usual tests for vitamin A *(29)*. The possibility of the presence of appreciable amounts of inhibitory vitamers of vitamin A is also indicated by the growth retardation in rats fed fish oils at a 15% level in the diet, despite adequate vitamin A; however, this effect is counteracted by yeast *(351)*.

Many different varieties of sharks have been tested as sources of vitamin A, as witnessed by reports from Fiji *(45)*, India *(112, 195)* and Uruguay *(122, 266)* among the many others. The liver oil of sawfish has also been studied *(195)*.

*Function of vitamin A in marine life.*—Visual purple mechanisms in marine forms have interested a number of workers *(31, 338)*. Carotenoids of the skin and eyes of 62 species of marine fish in Swedish waters have been studied *(185)*; surprisingly, selachians living at great depths are relatively lacking in these pigments. The porphyropsin-vitamin $A_2$ visual system appears to be a development of fresh-water teleosts, while elasmobranchs and nearly all marine teleosts have the rhodopsin-vitamin $A_1$ cycle. Migrant forms like the lamprey *Petromyzon marinus* contain both vitamins $A_1$ and $A_2$ in the retina, with the latter predominant *(339)*. Liver oils contain vitamin $A_1$.

Pigments of marine organisms have been exhaustively studied and cannot be reviewed briefly; there is a paucity of pharmacologic information despite a tremendous amount of chemical and physicochemical work. Karrer *(162)* has reviewed the carotenoids of tunicates, coelenterates and echinoderms, and a more recent review has appeared *(288)* on pigments of marine invertebrates, with an extensive statistical analysis. Special interest is attached to effects of echinoderm pigments on developing eggs (*v.* discussion on Hormones); pigments from *Halla parthenopea* and *Sphaerechinus granularis* increase respiration

of sea urchin eggs and rabbit erythrocytes some 15 to 20 times *(106)*. Xanthopterin is rapidly effective in anemia of fingerling salmon *(285)*.

*Thiamine.*—Thiamine is present in Atlantic crab meat *(99)* and oysters *(344)*; it is low or lacking in canned shrimp *(218)*. The etiology of athiaminosis from feeding raw smelt, herring or carp has been discussed under the use of marine products as foods.

*Other B vitamins.*—Riboflavine distribution is reported in 37 fish and fish products; fish meal is a rich source *(42)*. Riboflavine is found in various crustacea *(61)* and Atlantic crab meat *(99)*. The niacin content of 20 Bengal fish is noted *(271)*; it is present in fish, prawns and crabs *(164)*. Pyridoxine is found in the liver of cod and other fish *(189)*. Aside from choline, growth-promoting substances from marine sources have not, to our knowledge, been identified with other recently described members of the B complex.

*Ascorbic acid.*—Vitamin C is demonstrable in 14 marine algae *(190)*, in marine invertebrates *(118)*, crab meat *(99)* and fish *(103)*. Among the crustacea, *Paramysis helleri* and *Parenosa* are particularly rich in vitamin C *(275)*. The brain of the plaice contains about 3 times as much ascorbic acid as is present in other fish *(103)*. Von Euler *(334)* found considerable vitamin C in fish and marine invertebrates; in fish, it is present in largest concentration in the lens of the eye and in the viscera.

*Vitamin D.*—The usual sources of vitamin D among the fish oils include the liver fats of the cod, halibut, tuna, shark and percomorph fish. Exploration for other sources has paralleled studies on vitamin A mentioned above.

The Black Sea dolphin *Delphinus delphis* and the seal *Phoca capsica* have vitamin D in their fat *(200)*. The liver oil of *Paulicea lutkeni*, the jahu fish, is as rich as codliver oil in vitamin D *(100)*. Liver oil of the hammerhead shark *Sphyrna zygoena* contains 30000 U/100 g. *(313)*. *Myrtilus planulatus* is a good source of provitamin D *(98)*. The source of vitamin D in fish has been considered *(43)* with reference to possible

synthesis and the lack of effect of irradiation. Vitamins $D_2$ and $D_3$ are present in tuna liver oil *(54)*.

The sterol fraction of many marine forms has been examined chemically. These forms include coral *(215)*; a red sponge *Microciona prolifera (38)* and other sponges *(39)*; *Sepia officinalis* and sea urchins *(82)*; starfish *(36, 40)*; oysters *(34)*, *35, 37)*; and mussels *(37)*. Presence of ergosterol and dehydroergosterol in marine life has been noted, especially in the lugworm *Arenicola marina (117)*.

*Vitamin E.*—This vitamin is said to be present in various marine algae *(217)*.

*Vitamin K.*—The occurrence of vitamin K deficiency in chicks fed fish meal, and its cure by feeding moist fish meal which has been allowed to stand *(15)*, contributed to the early knowledge of this vitamin and its isolation.

*Other uses of fish oils.*—Effects of codliver oil on wound healing, the use of Na morrhuate in sclerosing veins, and chemotherapy of tuberculosis and leprosy with fish oil derivatives are mentioned by Sollmann *(294)*. The Council on Pharmacy and Chemistry of the American Medical Association reported that evidence available in 1943 did not justify topical use of codliver oil for wound healing *(76)*. Lesser *(181)* has more recently reviewed external uses of codliver oil. Ross and Poth *(265)* report appreciable antiseptic activity of oxidized codliver oil, due, in their opinion, to formation of acrolein during oxidation. An extensive study of natural antoxidants in fish oils has been made *(44)*.

Turtle fat does not differ appreciably in any chemical way from other depot fats of related forms *(128)* and its use in cosmetics is irrational. The oil of *Ruvettus pretiosus*, the castor oil fish, is a potent cathartic *(192)*, even when injected into the bone marrow *(191)*.

Among derivatives of fish oils, the use of soaps as spreading agents in insecticides is well known. Whale oil soap is effective against gladiolus thrips *(93)*, but must be applied repeatedly since it does not kill the ova. Pharmaceutic properties of Na morrhuate have been reviewed *(292)* and related to its use as a sclerosing agent *(156)*. Cu morrhuate has been used as a

blocking agent and reticuloendothelial stimulant *(16, 220)*, particularly in chemotherapy of tuberculosis and leprosy. A soup of S. American fish is used by the Indians as a cure for leprosy; properties of the oil are claimed to resemble those of chaulmoogra oil *(62)*.

Zooerythrine, a fat-soluble pigment from *Carcinus moenus* and *Homarus vulgaris*, has been recommended *(323)* as an effective fat stain for histologic experimentation.

## Hormones

Emphasis in studies of the reasonably well identified hormones found in marine forms has been placed mainly with those of the anterior and intermediate lobes of the hypophysis. Considerable work has been done also on autonomic neurohormones and on extracts of the gonads. Occasional contributions have appeared dealing with other endocrine products, and a number of actions of organ extracts have been attributed to unidentified "hormones."

*Pituitary hormones.*—Extensive data are available on hormones of the neural and anterior lobes of the manatee *Trichechus inunguis (230)* and the porpoises *Tursiops truncatus* and *Prodelphinus pragiodon (115)*; other marine mammals also have been studied. *Ciona intestinalis*, among the tunicates, has a structure functionally equivalent to the hypophysis of higher forms *(24)* and its extract has oxytocic, pressor and melanophore-dilating properties *(25)*.

For teleosts, information on evolution of the pituitary is reviewed *(163)*. Gonadotropins in pituitaries of teleosts and selachians may be demonstrated by implanting the pituitaries only in females about to spawn *(332)*; a pituitary suspension induces ovulation in fish if injected intracranially, but not if administered intramuscularly or intraperitoneally *(116)*. Houssay *(149)* reported a comparative study of the diabetogenic action of pituitaries from different animals, including the fish *Merluccius hubsii* and *Micropogon opercularis*; he found a rather small effect with these forms. Removal of the intermediate lobe does not influence pancreatic diabetes in the dog-

fish; it is believed that intermedin and the diabetogenic hormone of the dogfish are not identical *(5)*. Sea water extracts of the eyestalks of *Uca pugilator* and *Callinectes sapidus* are diabetogenic in the latter species; the diabetogenic factor is localized in the sinus gland of Hanström *(6)*. The pigeon crop test for prolactin is given after implantation of pituitaries of *Ameiurus nebulosus* and *Eupomotis gibbosus*, but not of mackerel, perch or codfish *(179)*. Another effect of marine products on lactation is the decrease occasioned by feeding codliver oil *(203)*, shark liver oil *(269)* or menhaden oil *(57)* to cows, or herring oil to goats *(123)*; salmon oil does not decrease secretion in cows *(203)* and shark liver oil decreases only the fat content, not the volume *(269)*, whereas codliver oil *(203)* and herring oil *(123)* are inactive after hydrogenation.

*Melanophore hormone in fish.*—Parker reported the hormonal control of melanophores in elasmobranchs *(237)*, catfish *(238)* and *Mustelus canis (235, 236)*. Intermedin causes darkening and selachine causes blanching in the latter *(239)*. It was noted early that pituitary extracts of several fish *(290)* affect the erythrophores of *Scorpaena ustulata*. The pituitary hormones of *Fundulus* act on *F.* melanophores *(2)*. Melanophore hormone is also present in the hypophysis of *Gadus morrhua (208)*. In the eel *Anguilla vulgaris*, a melanophore-expanding hormone is present in the posterior pituitary and a contracting hormone in the anterior lobe *(340)*. The peritoneal melanophores of *Acheilognathus intermedia* act oppositely in response to light, as compared to dermal melanophores *(352)*; this presumably involves an adaptation of sensitivity to pituitary hormones. Color changes induced in fish by pituitary and epinephrine-like hormones have been reviewed *(321)*.

*Melanophore hormone in crustacea.*—The eyestalk hormone of various crustacea has properties resembling those of pituitary extracts in higher forms. Reviews are available *(55, 66)*. The eyestalk hormone affects higher forms, such as tadpoles *(246)*, and acts on frogs like pitressin to influence water uptake and melanophores *(124)*. It has no effect on the gonads of the rat *(172)*. The commissural ganglia of *Palaemonetes* and *Crago* contain the same hormone, but these ganglia do not yield it in

*Callinectes*, *Carcinus*, *Libinia*, *Pagurus* or *Uca;* the eyestalks of *Palaemonetes* and *Crago* annul the effect of this ganglion extract, but not the eyestalks of *Carcinus*, *Libinia* or *Uca (56)*.

Much of the work on eyestalk hormone has been done with *Uca pugilator*, the fiddler crab. The properties of this hormone which has been purified to a potency of 400000 *Uca* units/mg. *(3)* are described in detail *(4, 65)*. The *Uca* unit is that amount of crustacean eyestalk hormone in 1 ml. of solution, 0.05 ml. of which, when injected into each of 15 specimens of *Uca pugilator* blinded 2 days previously, will produce a response with an average duration of about five hours *(1)*. *Uca* dies at the next molt after eyestalk removal, but probably not through lack of eyestalk hormone, since death does not occur if the crabs are covered with water during molting *(166)*.

*Autonomic neurohormones.*—Many physiologic studies have been made on the normal regulation of visceral functions in marine forms by choline esters and epinephrine-like substances; for the main, these are beyond the scope of this review. Representative studies show the presence of acetylcholine in ascidians, coelenterates, porifera and other forms *(22a);* isolation of acetylcholine as the chloroaurate from ganglia of *Octopus vulgarus (22b)*, and the cardiac effects of perfusates of *Octopus vulgarus*, *Sepia officinalis* and *Eledone moschata (315)* or of heart extract of the whelk, *Buccinum undatum* on *Raja clavata* and *Gadus morrhua (209)*. *Fundulus heteroclitus* scales destroy epinephrine, acetylcholine and atropine, but not mecholyl, pilocarpine or physostigmine; boiling inactivates these reactions *(48)*.

Of substances isolated from marine forms, the extract of the purple gland of *Murex trunculus* has received considerable attention. This is rich in choline esters *(326, 327)*. Toxicity of "purple" is due in large part to substances acting on the dorsal muscle of the leech; the corresponding "purple" from *Murex brandaris* is nontoxic to marine fish and has no effect on leech muscle *(160)*. "Purple" from *Murex trunculus* has also a curare-like action on the frog nerve-muscle preparation *(64)* and its toxicity is due in part to substances not destroyed by choline esterase *(49)*.

The limpet *Patella vulgata* contains a choline hydrosol which yields choline on autolysis, heating or enzymatic degradation *(161)*.

*Histamine-like substances; secretin.*—Histamine-like substances are demonstrable in most marine coelenterates, sponges, worms, echinoderms, crustacea and mollusks *(314)* and their content increases rapidly postmortem in marine fish muscle *(114)*. Haddock and lobster *(14)*, cod and mackerel *(13)* are effective gastric stimulants in the Armour pouch dog, and a broth of haddock skin activates the Pavlov pouch dog to 85% greater secretion than a broth of beef or haddock flesh *(169)*. Injured minnows, *Phoxinus laevis*, liberate from their skin a potent substance causing an alarm reaction in other minnows, unless the olfactory nerves are severed in the others *(335)*. This substance can be extracted with dilute acetic acid and contains 25 to 35 per cent N *(153)*; histamine base contains 37.83 per cent N *(206)*. Schooling in *Ameiurus melas* and *Morone labrax* has been shown by ingenious techniques to be dependent only on sight *(50, 299)*.

A comparative study on secretin showed little present in the alimentary tract of 2 fish *(170)*, but Bayliss and Starling found secretin in sharks and salmon.

*Extracts of gonads; related agents.*—Ovaries of the winter flounder, *Pseudopleuronectes americanus*, contain estrogens causing full estrus on vaginal administration of ether or acetone extracts to mature spayed mice *(90)*. Estrogens also are demonstrable in the ovaries of the sea urchins, *Lytechinus variegatus* and *Echinometria*, the holothurian *Stichopus mobii* and the lobster *Palinuris argus (89)*. Ovaries of herring do not contain enough estrogen to cause estrus in mice *(341)*.

Fish sperm contains a follicular stimulating factor *(71)*. Sperm of the oyster, *Ostrea virginica*, induces spawning; that of other mollusks is ineffective on oysters *(110)*. Oyster sperm also contains a "hormone" causing marked increase in flow of water through the gills of the same form, *Gryphea virginica;* this substance is called diantlin *(223)*. In contrast to the specificity of oyster sperm in causing spawning, eggs and glandular extracts of many other mollusks will cause release of sperm in

the male oyster *(111)*. In *Arbacia punctulata,* tissue extracts or injury will cause shedding of genital products; tissue extracts of *Fundulus, Asterias, Echinarachnis, Ostrea, Arbacia* itself, or frogs, are effective *(234)*.

Substances controlling respiration and growth of eggs have been extensively studied, particularly in the sea urchin. Eggs of *Urechis caupo,* a marine worm, contain urechrome which acts as a respiratory pigment *(147)*. Pigments from *Halla parthenopea* and *Sphaerechinus granularis* increase respiration of sea urchin eggs and rabbit erythrocytes some 15 to 20 times *(106)*. Crystalline echinochrome and spinochrome do not stimulate respiration of eggs or sperm of *Strongylocentrotus (310)* and the stimulation of *Arbacia punctulata* sperm by *A.* egg extracts is not due to echinochrome but to a higher alcohol produced by hydrolysis *(74)*. Eggs and larvae of sea urchins and starfish liberate a lipid inhibitory and a protein accelerating substance controlling growth; these have been partially purified *(243)*. Auxin is absent from eggs and sperm of *Discoglossus pictus, Arbacia punctulata* and *Paracentrotus lividus* and does not appear immediately after fertilization; auxin is developed suddenly during later growth *(264)*. An I compound resembling thyroxine, but much weaker, is present in testes and ovaries of *Echinus esculentus,* and is essential to fertilization; it may be Lillie's fertilizin *(68)*. The role in fertilization of agglutinins for eggs and sperm of *Strongylocentrotus purpuratus (311)* and the gamones, androgamones I and II and gynogamones I and II *(135)*, in *Echinocardium cordatum* and *Psammechinus miliaris (267, 268)* have been fully studied. The action of the gamones has been related to lecithinase activity; ultracentrifuge studies indicate a molecular weight of 2000–10000 for the agent in dialyzed sperm extract, and spectral analysis indicates the presence of a pyrimidine ring *(268)*. The gelatinous egg membrane was similarly studied, and electrophoretic measurements indicate a mucin; it is rapidly attacked by hyaluronidase of *Clostridium oedematis maligni* cultures *(268)*. Nucleic acids of sea urchin eggs have also been studied. Thymonucleic acid increases at the expense of pentose nucleoprotein during development of eggs of *Arbacia punctulata* and *Paracentrotus lividus*

*(52, 53)*. The unfertilized sea urchin egg probably contains some thymonucleic acid *(279)*. Among teleosts, the trout egg contains thymonucleic acid also *(316)*. Purine metabolism has been studied comparatively, with special attention to the tunicates; these resemble invertebrates in their purine metabolism and in lacking creatine, but are like vertebrates in their ability to perform certain methylations *(102)*. Guanine has special interest through its occurrence in guanophores of *Girella nigricans;* the amount present varies with the albedo of the background, suggesting a visual-pituitary control as with melanophores *(301)*. Guanine in *G. nigricans* is authentic, as demonstrated by the guanase test *(141)*. Spermine and spermidine are said to antagonize growth inhibition of *Escherichia coli* by quinacrine *(284)*.

The chemical composition of ovaries of the sea urchin *Sphaerechinus esculentus*, used as food in Peru, is reported *(150)*. Fish meal is said to contain a hatchability factor effective in chickens fed adequate riboflavine *(224)*.

*Hermaphroditism and secondary sex characteristics.*—Considerable work in this field has no immediate application to knowledge of sex hormones in marine forms, and is omitted from this review. Representative studies include the finding of living embryos in the scup *Stenotomus chrysops*, self-fertilized by teratologic hermaphroditism, and a literature review indicating that this condition is fairly common *(157)*. Castration of the prawns *Leander xiphias, L. squilla, L. serratus, Pandalina brevirostris* and others by parasitization with epicarids causes no sex reversal in males, but females fail to develop an incubatory chamber, which is taken to indicate the possible presence of a female sex hormone in these forms *(63)*. In *Xiphophorus helleri*, a teleost, ovariectomy and implantation of testes in females does not influence secondary sex characteristics *(317)*. To our knowledge, factors involved in the somewhat awesome sexual ambivalence of the oyster have not been elucidated.

Organ extracts of *Bonellia viridis*, a marine worm, are reputed to favor development of male from indifferent larvae; this effect is not due to the Cu content of the extracts *(221)*.

*Interrenal gland hormone.*—Interrenalectomy in *Torpedo ocellata* and *T. marmorata* causes death within 2–4 and 5–7 days respectively, with reduced respiration and contraction of melanophores; life is prolonged by cortical hormone *(88)*. Interrenalectomy in *Raja erinacea* has no effect on blood electrolytes but interferes with normal carbohydrate metabolism *(134)*. Grollman *(129)* has studied 3 species of skates and Santa *(274)* has more recently examined *Scylla canicula* and *S. catalus;* neither found epinephrine in the interrenal gland but note the presence of a hormone resembling desoxycorticosterone. Since the interrenals of *Scorpaena ustulata* and *Lophius piscatorius* contain chromaffin granules, they are not considered true interrenal glands *(85)*.

*Insulin.*—Due to the relatively complete separation of islet from acinar tissue in the pancreas of many fish, several workers early studied the hypoglycemic activity of extracts prepared from these 2 types of tissue in order to determine the site of insulin production in the pancreas. As a commentary on scientific prudence, it might be noted that none came to any definite conclusion although the results were reasonably clear-cut. Macleod *(194)* tested extracts from *Raja, Squalus acanthias, Myoxocephalus octodecimspinosus, M. scorpius, Lophius piscatorius, Zoarces anguillaris* and *Anguilla vulgaris* and suggested that the teleosts might furnish a practicable source of insulin. Others *(328, 329)* examined *Lophius piscatorius* and *Myoxocephalus bubalis;* and *Gadus callarius* and *Hippoglossus hyppoglossus (204)*. Jorpes *(159)* assayed the pentose and nucleic acid content of islets of elasmobranchs and *Lophius piscatorius.*

*Renin.*—On the basis of the finding of renin in glomerular kidneys of the catfish *Ameiurus nebulosus* and the carp *Cyprinus carpio* and its lack in the aglomerular kidney of the midshipman fish *Porichthys notatus,* it was suggested that renin formation is dependent on the glomerular or arterial components *(107)*. In marine fish having glomeruli, however, renin is absent; the sole and cod have none *(108)*. The difference in renin content appears to be related to habitat rather

than renal structure, since in the fish thus far studied the freshwater forms contain renin while the marine fish do not.

*Thyroid.*—The thyroid gland of the swordfish *Xiphias gladius* is particularly large *(11)*. The I content of the thyroid of *Raja laevis, R. erinacea* and haddock shows a clear sex difference *(60)*. The thyroid of lamprey larvae contains no I and does not stimulate metamorphosis of tadpoles *(148)*. Thyroids of *Scyllium canicula* and *S. stellare* accelerate metamorphosis of *Rana temporaria (283)*. The thyroid of *Scylliorhinus canicula*, an elasmobranch which never keratinizes its skin, will cause molting of the thyroidectomized lizard *Lacerta agilis* within 16 to 18 days after implantation *(282)*.

*Miscellaneous.*—The thymus of herring is reduced before maturity, but in rays and cod the thymus continues to grow *(180)*. Nephridia of *Physcosoma japonicum*, the skin and adjacent muscle, and the abdominal nerve cord yield a "hormone" causing acceleration of the rhythmic contractions of the nephridia; no epinephrine is present *(168)*. Sea water extracts of the branchial clefts of cephalopods contain a substance regulating circulation *(211)*. Alcoholic extracts of nerves, intestine, heart and gills of *Maia squinado* cause contraction of the intestines, heart and gills of the same form *(240)*. The hemolymph of invertebrates has an exciting action on the median ventricle of cephalopods *(26)*. Press juices of mussels or clams cause closing of the avicularia of *Bugula (105)*.

A 5% extract of the stomach of *Asterias rollestoni* decreases the amplitude of cardiac contractions in *Ostrea circumpicta;* a 50% extract causes irreversible damage. *Asteropecten scoparius* stomach is nearly as effective, that of *Aphelasterias japonicus* about half, and those of *Patiria pectenifera* and *Certonardoa semireguraris* are inactive. The tube feet of *Asterias* are about 0.1 as active as stomach; the digestive tracts of echinoidea and holothuroidea are not poisonous to *Ostrea (276)*.

## Immune Substances

A surprising number of contributions have been made in the field of immunochemistry of marine forms, disproportionately to the negligible significance of these matters clinically, in treat-

ing marine food allergies, dermatitis, and diseases of fish. Several references to fresh-water forms are included here because of their pertinence to marine problems.

*Agglutinins.*—Agglutination and hemolysis have been demonstrated in fish *(336)*. The development of agglutinins for sea urchin sperm in the carp is much more rapid at 28° than at 15° *(79)*; in trout, however, agglutinins against *Bacterium salmonicida*, which causes a furunculosis, are formed even at 10° *(291)*. Of interest in this regard is the finding *(357)* that gradual acclimatization to a hyperthermia of 32 to 35° has a prophylactic as well as a therapeutic effect on *Achromobacter ichthyodermis* infection of *Fundulus parvipinnis;* this organism causes an infectious dermatitis of *F. (342)*. Agglutinins have also been demonstrated in carp infected with *Pseudomonas punctata (249)* and in carp treated with a vaccine of these organisms *(250)*.

Eggs of *Strongylocentrotus purpuratus* are agglutinated by an agent extracted from eggs deprived of their surrounding jelly *(311)*. This agent is protein-like, species specific and probably identical with antisperm agglutinin extracted from sperm. Heteroagglutinin and isoagglutinins of *Echinus esculentus* have been studied *(68)*. Further reference to these agents is made above in the discussion of hormones affecting fertilization.

*Complement.*—The complement content of carp serum increases on adaptation to salt water, while the reverse is true in the eel *(91)*. Complement fixation has been studied in a number of related forms *(300)*. Fertilizin from *Strongylocentrotus purpuratus* is a strong anticomplement *(312)*; antifertilizin does not act as complement but does cause release of complement when mixed with bound complement.

Hemolysins of *Anguilla vulgaris* and *Tinca vulgaris* resemble the immune hemolysins of mammals in that they are composed of amboceptor and complement *(222)*. The Forssman antigen has been recognized in the Percidae *(300)*.

*Precipitins.*—Precipitin tests have been made on various related marine forms, mainly for their taxonomic interest. Reactions of antisera to *Homarus, Callinectes, Carcinus, Cancer, Menippe, Geryon, Ocypode,* and *Maia squinado (51)* are illus-

trative of taxonomic studies with this test. Among the simple invertebrates, relations of *Nereis virens* (Annelida); *Limulus polyphemus* (Arthropoda); *Asterias forbesi* (Echinodermata); and *Busycon carica, B. canaliculatum* and *Pecten irradians* (Mollusca) have been studied *(345);* the mollusks were closest to the annelids in their reactions. The importance of using lipid-free antigens for clear-cut tests is stressed. Hooker *(143)* finds greatly delayed sedimentation in titration of precipitins with hemocyanins of *Limulus polyphemus* and *Fulgur carica.*

*Other immune bodies.*—A tuberculin-like agent produced by growth of *Mycobacterium marinum* in broth will cause erythema and edema at the site of injection in marine fish infected with this organism *(20)*. Salt solution extracts of seaweeds commonly used in Japan as food will sensitize guinea pigs to later injections *(303)*. Control of infection of fish by marine algae such as *Thallamoeba parasitica (255)* may be through immune reactions. Immunity to glochidial cysts *(18)* and trematodes *(225, 226)* has been studied in fish.

In food allergies, there has been extensive study of a common antigen in crustacea: lobster sensitizes to crab and shrimp; shrimp sensitize to crab; and the crab lacks both lobster and shrimp allergens *(308)*. Extremely dilute herring extract will cause urticaria in sensitive patients *(183)*. The intestinal fluke *Nanophyetus salmincola,* found in salmon causes infections in Canidae; on recovery, immunity to further infection is present, but artificial immunity cannot be established *(286)*.

Antivenins are demonstrable in blood by injection of venom of *Vipera aspis* and *Cerastes cornutus;* among *Murena helena, Conger vulgaris, Trachinus draco, Scorpaena porcus, Uranoscopus scaber, Labrus maculatus, Serranus scriba, Deplodus annularis* and *Pagellus mormyrus,* only those with venomous blood are not susceptible to the snake venoms *(247)*.

Red moss dermatitis from sponges occurs in fishermen *(75)* and an acute cutaneous cellulitis may result from infection with *Erysipelothrix rhusiopathiae* from handling fish, shrimp or crabs *(263)*. Salt water rash has been noted in the discussion of sea water.

An antianaphylactic action of Na morrhuate and other soaps has been claimed *(248)*.

### Blood Coagulants and Anticoagulants

Muscle extracts of *Scylliorhinus stellaris* and *Conger vulgaris* contain a thromboplastin effective in clotting oxalated rabbit plasma *(358)*.

The autolysate of the hepatopancreas of *Ligia exotica* is anticoagulant for *L.* blood but clots the blood of common crabs *(229)*. Charoninsulfuric acid, obtained as its Ca salt from the hypobranchial glands of *Charonia lampas*, is a more powerful anticoagulant than heparin *(199)*. This agent probably resembles heparin in structure *(293)*. It is probable that similar agents might be obtained from parasitic marine forms.

Carrageen jelly is said to be an effective anticoagulant *(86)*. An extract of *Delessaria sanguinea*, an alga, will render rabbit blood incoagulable for 1 hour when 15 mg./kg. are injected intravenously; it is also effective by mouth. Its action is antagonized by injection of 2 mg./kg. of thionine *(97)*.

### Enzymes

Dry enzyme preparations from the stomach and different parts of the intestine of the cod, haddock, hake and mackerel have been tested for tryptic activity *(158)*. Intestinal enzymes of the carp have also received considerable study *(278)*. Interest in enzymes of fish has been mainly directed toward their use in tanning leather.

*Sepia officinalis* contains amine oxidase in various tissues; this is specially active in the oxidative deamination of tyramine *(46, 47)*. The homeopathic use of sepia as an adrenal stimulant is rationalized by Gutman *(131)* on the basis of its dopa oxidase content.

Enzymatic hydrolysis leading to decay of wood pilings is caused by hyphae of various marine fungi *(28)*. The destructive role of crustacea on submerged timber is also of great economic importance *(154)*.

### Nitrogen Extractives

N compounds from different marine forms have been carefully examined chemically. N extractives of teleosts, selachians,

crustacea, mussels, worms, sea urchins, anthozoa and sponges *(174)*, the jellyfish *Cyanea capillata (213)* and *Velella spirans (138)*, the sardine *(92)*, *Eledone moschata (9)*, the scallop *Pecten magellanicus (216)* and the liver *(10)* and muscle *(214)* of *Acanthias vulgaris* are among the many which have been studied. Occurrence of a number of pharmacologically interesting bases has been noted: guanidine in marine invertebrates *(95)*, anserine and carnosine in selachians and teleosts *(8)*, hypoxanthine in embryos of *Acanthias vulgaris (296)*, protamines and histones *(350)*, taurine in mussels *(80)* and abalone *(245)*, N compounds in the stomach contents of the sperm whale *(302)* and trimethylene oxide in lobsters *(144)* and other marine forms *(145)*. The latter compound yields trimethylamine when certain bacteria act on it, and this reaction may be used as a rapid method for differentiating typhoid and dysentery groups *(27)*. N bases formed on decomposition of algae are highly toxic to Atlantic salmon *(210)*. Large scale destruction of marine life may be caused by these agents together with $H_2S$ formation and O-lack in sea water involved in phenomena such as the Callao painter of S. America *(205)*.

Amphiporine has been isolated from *Amphiporus lactiflorens*, *Nemertinea amphiporus* and *N. drepanocophorus (23,165)*. This agent has a strong nicotine-like action on the frog rectus abdominis muscle when applied 1:1000. Nemertine, isolated from the nemertine worms *(23)*, excites the crab nerve-muscle preparation.

Macht *(193)* reports the phytotoxic properties of muscle extracts of 65 fish, of which 10 were active against lupine seedlings and mice. Vasomotor paralysis follows intravenous injection of 1.2 ml/kg. of blood serum of the sheatfish *Siluris glanis* in rabbits *(333)*. Mussel poison from *Mytilis californianus* has been purified *(33)* and studied pharmacologically *(252)*; this poison does not affect respiration of the mussels themselves *(343)*. Colby *(73)* and Levrat *(182)* review skin reactions to and wounds from various marine forms, including jellyfish, *Trachinus*, *Strongylocentrotus lividus*, *Toxopneustes*, sea anemones, *Talitrus saltator*, the tubeworm *Serpulus*, and the Portuguese man-o-war; unpublished chemical studies of

Bodansky are cited *(73)* for the latter organism, on the nature of nematocysts and hypnotoxin. The acrid secretion of the repugnatorial glands of *Onchidium floridanum* is said *(19)* to contain acid-bearing protein granules and unidentified soluble substances. Toxins may play a part in the reaction of the crab *Pagurus pubescens* to parasitization with *Peltogaster paguri (262)*. The chemistry of the poisons of *Scorpaena porcus* and *Octopus vulgaris* has been studied *(187, 309, 325)*. Chemical and pharmacologic studies have also been applied in demonstrating the absence of poisons in certain forms, as in *Trachinus draco (78)*. Taft *(305)* discusses the status of some of the less well identified marine "poisons."

### Miscellaneous Items of Pharmacologic Interest

The marine hydroid *Obelia geniculata* has, as its prime growth controlling system, an –SH equilibrium mechanism which makes convenient a study of this metabolic means in a simply constituted organism *(132)*. Gradients may be easily studied in simple marine forms such as the starfish *Patiria miniata (70)*. The glutathione content of many marine animals is known *(295)*. Bioluminescence of certain marine microorganisms and the luminous organs of fish may serve *(136)* indirectly in pharmacologic investigations as far afield as chemotherapy and the pharmacodynamics of narcosis.

Normal regulatory mechanisms and metabolic processes of marine organisms have been touched upon only incidentally in this review, but there are many interesting studies beyond the evident problems in autonomic control and comparative biochemistry. As an example, the narcotic effects of high tensions of $CO_2$ in mammals *(178)* have a corollary in the self-narcotization of oysters by $CO_2$ on induced prolonged closure of the valves *(253)*; this effect has actual commercial value in facilitating preparation of oysters for marketing.

### Discussion

The lack of application of substances from marine sources to medicine, aside from those materials which have proven their worth over the years (I, Mg and Br compounds, agar, fish

oils), is due more to lack of study of the highly potent agents available and search for others than to a paucity of pharmacologically interesting substances from the sea. There is little doubt that if the chemical isolation of insulin had been more difficult to perfect, fish would constitute a major source since their islets are readily obtained essentially free of acinar tissue. The search for antibiotics more satisfactory than penicillin has not, to our knowledge, been extended to marine forms, although *Chlorella vulgaris* and *C. pyrenoidosa* yield an antibiotic *(251)*. If present studies of physiologic effects of intermedin lead to clinical use of this hormone, it is possible that crustacean eyestalks might be an important source.

Use of marine products in medicine shared the fate of the general materia medica when therapeutic nihilism reduced the number of all drugs in use to a few of demonstrable value. Whereas considerable progress has since been made in developing rational therapeutic agents through chemical synthesis and collaborative botanical and chemical studies, the science of marine biology has been virtually neglected as a possible contributor to better therapeutic means.

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## Summary

Pharmacologically active agents from marine sources are reviewed in relation to the historical background of marine drugs, properties of sea water, active agents in algae, and the following groups of medicinal agents found in marine organisms: inorganic substances, nutrients, vitamins, hormones, immune substances, blood coagulants and anticoagulants, enzymes, various N extractives and miscellaneous agents. The present status of drugs from marine sources is briefly discussed.

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# POISONOUS MARINE ANIMALS*

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The poisonous marine animals may be divided into two groups: those that are poisonous when eaten and those that are venomous. A fairly exhaustive study of the literature on this subject has been conducted, but no claim for completeness is made.

## VENOMOUS MARINE ANIMALS

The forms that are venomous are many. Some of these, the Coelenterates, are equipped with stinging cells, nematocysts, as in the jellyfish. In cool and temperate waters these stings are painful but not serious. There have been several deaths due to jellyfish stings reported in tropical waters. Stuart and Slagle (1943) stated that although several species of jellyfish have stung bathers in the tropics, the symptoms in all cases are the same, a burning pain at site of contact with redness followed by a wheal; muscle spasms of rapid onset involving trunk muscles; flushed skin, dilated pupils; congested respiratory mucous membrane; profuse thin secretion from mouth and respiratory tract; lacrimation; almost constant productive cough; difficulty in respiration due to spasm of respiratory muscles; anxiety; fear; and marked pain in abodomen and back due to violent muscle spasms. Local application of alkalis give practically no relief, but adequate doses of morphine or calcium gluconate given intravenously will afford relief. Upon recovery, the symptoms persist for only a few hours. Wade (1928) reported on the post-mortem examination of one such case; it was found that death had been due to "suffocation" although the body never had been submerged. There was "general visceral congestion and status lymphaticus." Old (1912) gave clinical reports on several cases.

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Colby (1943) stated that the nature of the poison from the Portuguese Man O'War (Physalia pelagica) was investigated by the late Meyer Bodansky who discovered "(1) Injection of extracts from the tentacles into pigeons causes coma, respiratory paralysis and death, (2) the extracts caused a local dermatitis like that of the fresh tentacles and if this was severe enough fever resulted, (3) the dried extract remained active for as long as two years, (4) the poison is easily destroyed by heat or trypsin. . . ." Bulletin of the United States Army Medical Department (1944) states that some species of Corals are venomous.

The sea anemone (Anemone scultata) contain two poisonous substances, thalassin and congestin (Richet, 1902, 1903, 1904). Thalassin on contact causes intense itching and even urticaria. Thalassin may be obtained in crystalline form, and when injected into a dog intravenously 0.1 Gm./kg. produces sneezing and erythema with intense congestion of the mucous membranes. Congestin in the dose of 2 mg./kg. killed dogs in twenty-four hours. Congestin sensitizes animals to thalassin whereas thalassin renders animals insensitive to congestin.

There are the poisons from sea anemones that cause a disease of sponge divers in the Mediterranean (Calmette, 1908). Zervos (1903) and Stitt (1942) said that the disease (la maladie des plongeurs) is observed in men who dive naked. The anemones live at the base of sponges and secrete a viscid substance. The first symptoms are itchings; a papule appears at the site of contact and soon is surrounded by a red zone and in a few days the skin sloughs off leaving a deep suppurating ulcer. The onset of the disease is accompanied by fever. Pawlowsky and Stein (1929) experimented with an extract from Actinia equina and reported that when this was applied to the skin there was inflammation, engorgement of vessels, edema and an increase in the lymphocytes and polymorphonuclear leukocytes.

One menace of the beaches of the South Seas is the mollusk, the poison cone shell, Conus. Several species of this genus are poisonous. If one were to pick up the shell containing the living animal the radula might pierce the palm of

the hand or one of the fingers, thereby introducing the poison of unknown nature into the wound. The symptoms are said to resemble curare poisoning (Clench and Kondo, 1943).

Several cases of poisoning have been reported as due to penetration of the spines of echinoderms through the skin. Some of these deaths doubtless were due to bacterial infection (Swan, 1887) but at least in the cases of the "Giant Star Fish" reported by Miner (1938) and the sea urchin, Centrechinus setosus, reported by Earle (1941), there seems no doubt that some sort of a toxic substance is introduced into the body. Henri and Kayolof (1906) reported that a pulp made from pedicellariae of Sphaerechinus granularis produced death from asphyxia in a rabbit.

Along the Great Barrier Reef there is a worm about a foot in length that, according to Roughley (1940), is protected by sharp white spines. If the worm is picked up, even when thick leather gloves are worn, these spines will enter the fingers. At first there is irritation which is followed by numbness lasting six weeks.

Some venomous fish are provided with poison glands and inoculatory organs such as spines, while others have a poison fang apparatus similar to snakes (Calmette, 1908). Most of the venomous teleostei are sedentary in habit.

With the exception of those fish provided with poison fangs, the venom usually is located in special glands at the base of the fins or spines. When these spines pierce the skin the fish ejects a toxic or irritating substance which enters the wound.

Scorpaeniformes (Scleroparei)—Goodrich (1909)—appear to have developed from a primitive perch-like form. Several families of this subtribe are venomous. The family Triglidae includes the stonefish, Synanceia verrucosa, a very venomous fish found among the coral of the Great Barrier Reef of Australia (Whitley, 1943; Chute, 1941; Roughley, 1940; U.S. Army Medical Bulletin, 1944). This, or closely related species, is found in the warmer regions of the Indian and Pacific Oceans (Calmette, 1908). If the fish is stepped on with a bare foot, very painful and sometimes fatal poisoning results. Along the coast of Normandy, members of the Cottidae are feared

by the fishermen on account of their painful sting. The nature of the poison of this group of fishes is not known. The family Scorpaenidae often has the dorsal spines provided with poison glands (Goodrich, 1909). Various species of this family, Scorpaena atlantica, S. Ginsbergi and S. Brasiliensis, are found in the Gulf of Mexico (Colby, 1943), and many other species are found in the warmer waters of the various oceans. The poison apparatus is situated in the spine rays of the dorsal and anal fins (Calmette, 1908).

The Weevers, genus Trachinus, are found in European waters, according to Calmette (1908). They possess two sets of poison apparatus—one on the operculum and the other at the base of the spines of the dorsal fin. Each spine has a double cannelure. Briot (1902, 1903, 1904) isolated some of the poison. Two or three drops injected intravenously into a rabbit causes death from asphyxia in four to ten minutes. The heart continues to beat after respiration ceases. There is no relationship between this venom and the venom of cobras. Gressin (1884) described the symptoms in man as being first a violent, shooting pain, the limb becomes swollen and inflamed and is accompanied by fever and delirium. This syndrome may last for two to three hours or for several days.

Several venomous Gobiidae are found along the coasts of France and in tropical waters (Calmette, 1908). Apparently they do not bother people very much.

The family Teuthididae, surgeon fish, has a compressed body and the tail is armed with movable lateral spines (Goodrich, 1909). These are brilliantly colored fish and are found in tropical waters. The stings and cuts from these fish may be painful but usually are not serious (Calmette, 1908; Whitley, 1943).

There seems to be some confusion as to which members of the Betrachidae are venomous. Goodrich (1909) and Froes (1932) stated that Thalassophryne is provided with poisonous glands and spines. Calmette (1908) credited Batrachus (Opsanus tau) with being venomous. Nigrelli (1944) stated that the toadfish or oyster fish (Opsanus tau) has no poison spines. This probably is correct as no reports have been made

of poisoning from the handling of common toadfish (Opsanus tau) by laboratory workers along the Atlantic Coast of the United States. The author has handled hundreds of these fish and has had his hands pierced by their spines many times but with no more discomfort than would be expected from the prick of a pin or any other fish. There were no signs of systemic reaction.

Catfish (Siluroidae) contains the marine families Ariidae and Plotosidae which are found in tropical waters and the Indian and Pacific Oceans (Enc. Brit., 1932). These fish have dorsal and pectoral fins capable of inflicting severe and sometimes poisonous wounds (Whitley, 1943; Calmette, 1908; Colby, 1943).

The Muraenidae (Morays) are provided with very formidable teeth pointing backwards. The pectoral fins and girdle may be lost (Goodrich, 1909). The body is scaleless and usually brightly colored. These large eel-like fish have a poison apparatus connected with curved teeth by which the venom is introduced into the wound (Calmette, 1908; Nigrelli, 1944). These fish are greatly feared by fishermen and icthyologists consider them very dangerous. (Colby, 1943; Simmons et al., 1944; Bull. U.S. Army Medical Department, 1944).

The venomous Selachii are both sedentary and active in their habits. The electric rays, or Torpedinidae, are common in warm waters; they are equipped with organs capable of generating considerable electricity and thereby giving the person who comes in contact with them a very unpleasant shock (Shultz, 1938, and many others).

The sting rays belong to the family Trygonidae and are also found in warm seas. They are provided with one or more large serrated spines on their tail which has lost its fin-like character (Goodrich, 1909). Evans (1916, 1924) presented evidence to show that these fish are venomous. Schultz (1944) and Gudger (1943) corroborated this. Macht and Spencer (1941) believed that they produce a poisonous substance demonstrable in their muscle juice. The Spiney Dogfish (Squalidae) has two dorsal spines anterior to the fin with

a groove lying against the anterior margin of the fin. This groove is occupied by a secreting gland from which the poison exudes. Wounds made by these elasmobranches are painful and may require a week's hospitalization. The Port Jackson Shark (Heterodontus) has dorsal spines of the same general character as the Dogfish. The Chimaeras (Chimaeridae) also possess poisonous spines (Evans, 1944).

There are many other species of fish that are reported to be venomous, but in most cases the venom has not been demonstrated. The actual wound produced by the fish is painful and dirt and bacteria are introduced by the piercing organ into the wound. In many cases it is probable that infection has caused the symptoms that are blamed on a mythical venom.

### Venomous Marine Reptiles

Sea snakes of the family Hydridae live in the tropical regions of the Pacific and Indian Oceans. There is one species found along the Pacific Coast of Central America and in the Gulf of California. These snakes are extremely poisonous but seldom attack man unless handled, the chief danger being in handling them in fish nets. The poison in general resembles that of the cobra. There are several genera divided into 50 or 60 families (Cochran, 1943; Ditmars, 1943). They are not found in the Atlantic Ocean.

### Marine Animals Poisonous When Eaten

Many marine forms are credited with being poisonous when eaten; in some cases there can be no doubt that some sort of an endotoxin is developed. In other cases it is extremely doubtful if the form is poisonous. Most marine animals spoil very rapidly unless well refrigerated and are easily contaminated by the "food poisoning" bacteria. It should also be remembered that many persons are allergic to sea food. Many of the early writers on this subject did not distinguish between illnesses caused by bacterial decomposition or some infection of the fish and those caused by a toxin produced by the fish.

In this review it is intended to mention only those cases of illness produced by a toxin. Due to some tradition, several forms that would appear edible are not eaten at all, or only during certain periods of the year. One wonders if there is any scientific basis for these taboos. Oysters collected during July and August in Buzzards Bay were as appetizing to the author as those collected during the "R" months and had no unpleasant effects. Their collection is reported to be forbidden in France during the summer due to the presence of a toxic substance (Emerson and Taft, 1945). Jordan and Gilbert (1882) mentioned that several fish found in the vicinities of Pensacola and Galveston are not used for food, but they give no reason for this.

Calmette (1908) stated that sea anemones are poisonous when eaten and that the animal eating them dies of convulsions in a few minutes. The ova of many sea urchins are credited also with being poisonous when eaten (Stitt, 1942).

Eating the edible mussel (Mytilus californianus) has caused many cases of serious illness and deaths (Stitt, 1942). Prinzmetal, Sommer and Leake (1932) isolated and described a very toxic substance from mussels. Sommer, Whedon, Kofoid and Stohler (1937) contended that the poison is in the mussel due to its having ingested a dinoflagellate (Gonyaulax catenella) which is poisonous. Sommer and Meyer (1941) thought the poison was an alkaloid. The poison from this dinoflagellate has been found in other plankton feeders, such as clams and oysters (Sommer, 1939). "Mussel poisoning" has been known for more than one hundred years. Several cases occurred in California in the nineteen twenties; more recently cases have been reported along the northern Pacific coast of the United States, from the Bay of Fundy and Belgium. Gebhard, Collier and White (1939) reported two deaths from "mussel poisoning" in Digby County, Nova Scotia. Cases have been reported as a result of eating clams collected in the Gulf of California (Sommer, 1939). Various plankton feeders ingest the dinoflagellate and develop a condition which Sommer (1939) and Sommer and Meyer (1937) called "paralytic shell fish poison-

ing." Persons who eat these "sick" marine forms are stricken with "mussel poisoning."

Smith (1933) reported that the flesh and eggs of Carcinoscorpius rotundicauda (a horseshoe crab) are poisonous to man.

Most authors (Simmons et al., 1944; Colby, 1943; Whitley, 1943; Stitt, 1942; Seale, 1912; Keer, 1912; MacGowan, 1886; Tybring, 1885, and others) agree that fish of the Tetrodon family are potentially dangerous. These are the balloon fish, puffer fish, pipe fish, etc. They lack the usual scales and are usually spiney. This group is widespread and its members are known under many different names. In Japan these fish are known as Fugu. Tokushi and Tani (1937) reported 909 cases of fatal Fugu poisoning in Japan in a ten-year period ending 1937. Poisoning has been reported from almost all parts of the world. It is claimed by some that these fish are poisonous only during the spawning season when the toxin is mostly in the gonads. Others claim that they are poisonous all the time and that the toxin, while mostly concentrated in the gonads, is spread throughout the entire body. The general consensus of opinion is that to be safe one should never eat the non-scaly fish. The relationship of poisoning by non-scaly fish to Hebrew dietary laws has been dealt with by D. I. Macht (1942).

Tahara (1910) has described a method of extracting the toxin from the ovaries of the fish. The approximate formula given was $C_{16}H_{13}O_{16}N$. According to him the toxic dose was 0.0041 mg./Gm. mouse and 2.5 to 4 mg./kg. rabbits. Toxicity is readily destroyed by mineral acids and alkalis. In 1913, Tahara described tetrodotoxin as a white, amorphous, odorless, tasteless substance, soluble in water, only slightly soluble in alcohol and insoluble in absolute alcohol, ether and other organic solvents.

Inouye (1913) stated that large doses of tetrodotoxin cause paralysis of motivation. Strangury, caused by injecting silver nitrate into the bladder of dogs, ceased after subcutaneous injection of one-half the lethal dose of tetrodotoxin. It seems to have a beneficial effect in cases of enuresis nocturia. According to Kariya (1911), it has no cumulative action.

Ishihara (1919) said that it was a crystalline compound and a powerful nerve poisoning agent acting chiefly on the sympathetic nervous system, leaving the myoneural junctions intact. On injection it produced a fall in blood pressure and a circulatory slowing. There was marked fibrillation and heart block finally occurred. Through its interference with the sympathetic nerves, peristalsis was quickened and secretion of perspiration and saliva was inhibited. Death probably resulted from direct action on the respiratory center. In concentrations of two parts per million it paralyzed a nerve fiber in half an hour, and striated muscle in one and one-half hours. It had little action on the stomach, intestines, blood vessels, iris or bladder.

Larsen (1939) extracted a white crystal, the salt of tetrodonic acid, from the eggs of the balloon fish. It was dialyzable from a solution of the eggs. It has the following characteristics: very soluble in water, slightly soluble in alcohol and insoluble in ether. Boiling for several hours in 95 per cent alcohol did not destroy it, nor is it destroyed by air-drying or sunlight. Mouldy samples several months old gave characteristic toxic symptoms. Dry heat at high temperatures destroys it in fifteen minutes. Extracts from various portions of the fish were injected into animals with the result that extracts from the eggs were always fatal and extracts from the bile, kidney, liver, intestinal content and urine may be fatal and extracts from the flesh rarely were fatal.

Closely related to the Tetradons are the Diodontidae, the Balistidae and the Monacanthidae; in general their poisoning action is essentially the same as that of the Tetrodontidae (Seale, 1912; Colby, 1943; Whitley, 1943; Simmons et al., 1944). In the groups of fishes so far discussed there is definitely an endotoxin.

Some members of the Carangidae (Amber Jack or Seriola fasciata); Yellow Jack (Caranx bartholomoei); Skip Jack (Caranx ruber) and Horse-eyed Jack (Caranx latus) are credited with producing an endotoxin, but this has not been definitely demonstrated. When poisoning from these fish occurs it is in regions where, for the most part, the facilities for

proper handling of the fish do not exist, so the illness following their ingestion may be some type of food poisoning. Such instances of poisoning have been reported mostly from the Virgin Islands and some of the West Indies (Gillman, 1942; Mann, 1938; Tybring, 1885; Walker, 1922; Gregory, 1925). In some localities these fish are considered excellent food, but in others, to be extremely poisonous. The larger fish are considered more dangerous and the poisoning is more or less seasonal and probably connected with the spawning season. O'Neill (1938) reported poisoning from eating the roe of the Amber Jack.

Several species of Melatta (Clupeidae; Herrings) are reported as being poisonous. When they are eaten, powerful cramps, with dyspnea, cyanosis, cold sweats, dilated pupils and sometimes death, may follow. Melatta venenosa (Simmons et al., 1944; Stitt, 1942; Tybring, 1885) and Culpea venenosa (Simmons et al., 1944, and Seale, 1912) are among the species implicated. These are found in both the Atlantic and Pacific Oceans.

Gillman (1942) and Mann (1938) claimed that the kingfish, Scomberomorus cavala, a member of the Mackerel family, is poisonous. They report poisoning from the Puerto Rico-Virgin Islands area.

Whitley (1943) reported that while the flesh of the Goat fish or Red Mullet is delicious, wholesome food, eating of the brain causes convulsions (Simmons et al., 1944).

The Barracuda, especially the large ones (Simmons et al., 1944; Colby, 1943; Gillman, 1942; Seale, 1912; Tybring, 1885, and Gudger, 1930), have been listed among the poisonous fish. Mowbray (1916 and 1922) considered poisoning from this fish to be "ptomaine poisoning" due to improper handling and storing.

Colby (1943) quoted Coker (1930) to the effect that the roe of the Gars, Astractosteus spatula and Lepisoteus sp. are poisonous. Schultz (1938) reported that the eggs of the Marbled Sculpin are poisonous when eaten.

Macht and Spencer (1941) experimented with freshly expressed muscle juices of 65 varieties of fish. These were tested

by intraperitoneal injection into white mice and by studies of growth of Lupinus albus seedlings. The following were found to be toxic for mice and Lupinus albus: Catfish (Ameiurus catus); Eel (Anguilla chrisypa); Moonfish (Vomer setipinnis); Porcupine fish (Diodon hystrix); Puffer (Spheroides maculatus); Sand Skate (Pteroplatea maclura); Dogfish (Mustelus canis); Stingaree (Dasyatis say) and Toadfish (Opsanus tau).

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## Bibliography

Space and time do not permit the preparation of a complete bibliography on poisonous marine animals. However, it is possible to mention some sources to which the interested reader may turn for information.

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Dr. E. W. Gudger has written that a card catalog of references since 1923 has been kept by the museum, and also that Miss Margaret Titcomb of the Bishop Museum, Honolulu, has prepared a bibliography of the poisonous fishes of the Pacific.

Among the references cited, Simmons et al. (1944) and Larsen (1942) have fairly extensive bibliographies.

For lists of poisonous fish the reader is referred to Simmons et al. (1944); Seale (1912); Gilman (1942) and Mann (1938a). Mann (1938a) also has a short history of fish poisoning in the West Indies, as does Gudger (1930).

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# THE VAGARIES OF RH

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## *Early History*

The name "Rh" was given to a blood factor, when Rhesus monkey cells were first used as the antigen to produce the immune serum whereby a new blood antigenic factor was discovered. It seems that primarily the Rhesus macaque (Macaca mulatta (Zimmermann)) is usable as a source of antigen if anti-Rh serum is to be produced experimentally. New World Rhesus monkeys do not seem to be satisfactory.

It was due to the inquisitiveness of a clinician that one Rh antigenic factor was discovered. He asked the question, "Why do so many post-partum mothers receiving a transfusion die when the transfused blood seems compatible by all present known laboratory tests?" Levine and Stetson (1939) first described an atypical agglutinin and assumed it resulted from immunization of the mother by factors in the fetus which were inherited from the father. Landsteiner and Wiener (1940) were the first to note that the agglutinins prepared from Rhesus macaque cells were very similar to this particular atypical agglutinin found in the human. This atypical agglutinin clumped the red cells of about 85% of the white population tested, as did the experimental anti-Rhesus serum.

## LATER KNOWLEDGE AND PECULIARITIES OF RH

Our knowledge of the "vagaries" of Rh agglutinins and agglutinogens has increased remarkably in five years. It has been found that the agglutinogens are present as an integral part of the red blood cells in 87% of the white population and absent in 13% (Levine, 1941). About 92% of the colored population (of New York City) are Rh positive and approxi-

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mately 8% are negative. Of the small number of Chinese, Japanese and Mongolians tested, more than 98% are positive, leaving less than 2% negative (Levine, 1940). Even though two people are Rh positive, there are certain examples of isoimmunization occurring either by transfusion or pregnancy. Levine has shown this may occur, and further, that the chance for such sensitization is rather low. The question of homozygous and heterozygous characteristics of individuals increases our interest since the outcome of pregnancies are quite often dependent on these factors. It is only by knowing whether individuals are homozygous or heterozygous that we can understand why, by the same matings, some of the offspring live and others die as the result of Rh factor incompatibilities.

Some of the differences of the Rh factor, as compared to the common blood groups, are that the Rh agglutinins have not been found to occur normally in human serum. Beta and alpha agglutinins are known to be in the serum of types A and B respectively, but Rh agglutinins occur only after sensitization, regardless of whether the sensitization occurred by transfusion or pregnancy. There is also a larger number of Rh agglutinins and agglutinogens than of the common blood groups. Wiener (1944) recognizes 5 Rh agglutinins and 8 agglutinogens; Levine (1942, 1944) recognizes 4 typical Rh agglutinins and 1 atypical agglutinin (Hr) and 5 agglutinogens. The Rh agglutinins overlap somewhat as alpha and beta agglutinins in their abilities to clump red cells of more than one group. For example, alpha agglutinin clumps B and AB cells, and according to Wiener's new classification (1944), Rh′ antiserum clumps all Rh positive cells except the Rh″ cells. Other of the Rh antisera also agglutinate cells of more than one Rh phenotype; however, no single antiserum has yet been found which clumps all Rh positive cells. Theoretically, an antiserum which would clump all Rh positive cells could be produced by transfusing an Rh negative patient with $Rh_o'$ $Rh_o''$ cells, or a combination of cells with all known antigenic components. Such an antiserum, according to Wiener (1944), could not occur as the result of a single pregnancy, since the fetus would inherit either the $Rh_o'$ or the $Rh_o''$ factor, but not

both. The Rh factor is inherited as a dominant characteristic according to Mendelian law, and is not sex-linked.

For a time, only about 90% of the true cases of erythroblastosis fetalis could be accounted for by Rh incompatibility between mother and offspring. The unaccounted for 10% were found to be from Rh negative fathers and Rh positive mothers. Levine (1942) found an atypical agglutinin in the serum of one Rh positive mother (her mate was negative) which acted much differently from any other agglutinin then known. This atypical agglutinin agglutinated all Rh negative cells and a number of Rh positive cells, and he named it "Hr" since its action was the reverse of the familiar Rh agglutinin. Race and Taylor (1943) (in England) independently applied their term "St" to a similar agglutinin. It was found that the positive cells agglutinated by this serum were heterozygous Rhrh, and that the positive cells not agglutinated were homozygous RhRh. After investigating a series of bloods, Waller and Levine found that "about 60% of $Rh_1$ bloods of white individuals and almost all colored individuals tested possessed the 'Hr' factor." This would indicate that a majority of Rh positive people are heterozygous (Rhrh). With the discovery of the "Hr" agglutinin, Levine (1942) was able to account for all cases of erythroblastosis fetalis due to incompatibility of Rh groups.

## Methods of Sensitization or Immunization

Isoimmunization by transfusion is important to the Army since many of our casualties are receiving whole blood transfusions. It is not possible at present, nor is it the policy of the Army, to do mass Rh testing of military personnel, because there is insufficient typing material and likewise there is a scarcity of trained personnel to carry out the tests. The immediate objective in the theaters of war is to get blood to those needing it in the shortest possible time, and it is certain that many military personnel may be sensitized. After sensitization, it may be possible by careful work to prevent fatalities when subsequent transfusions are required, and this responsibility must not be side-stepped.

The Rh factor is an excellent antigen, but all humans do not produce demonstrable antibodies against it, even though repeated contacts with the antigen are made. It is true that sensitizations will occur, mainly, when Rh positive blood is transfused to Rh negative patients. It is possible to cause sensitization by transfusing an Rh positive patient with Rh positive blood whose antigenic characteristics are different; as an example, a donor with $Rh_o'$ blood may be capable of sensitizing a recipient of the $Rh_o''$ type. Until large quantities of all different anti-Rh typing sera are available, it is impossible to prevent such isoimmunization since Rh phenotype classifications are not routinely made. With respect to the person who is unfortunate and becomes sensitized to the Rh factor, he will always remain sensitized even though no agglutinin titer is demonstrable. A careful history of a previous transfusion or pregnancy is, therefore, of vital importance.

Sensitization through pregnancy is of increasing interest to the Army since many dependents of military personnel are delivered in Army hospitals. Many Army hospital laboratories are providing themselves with potent Rh typing material from obstetrical patients. It is thought that isoimmunization in pregnancy is produced in the following manner: Since there is no direct circulation between mother and fetus, an occasional placental villus breaks off and allows seepage of whole red blood cells from the fetus to the mother. It has been estimated that placed end to end the villi would extend approximately eleven miles, or if laid side by side would cover an area of about seventy square feet. It is known from histologic examination at postmorten that pieces of placental villi are found in the lung, thereby providing the suggestion that seepage of whole blood from fetus to mother is possible. Should both mother and fetus be of the same Rh characteristics there will be no sensitization; however, if the mother is Rh negative and the father Rh positive, the fetus will, in most cases, be Rh positive due to the dominant characteristics. Since the mother is Rh negative, she is capable of being sensitized to the Rh factor by

Rh positive cells from the fetus. The Rh positive cells of the fetus are picked up in the mother's blood stream and act as an antigen. This process may go on for several months, but it is an individual matter as to how strongly the mother may become immunized. It is not definitely known at what period of gestation the Rh antigen becomes an effective antigen. Macklin has suggested that the immunization of the mother may be associated with developmental stages of the fetal red cells, and that in the early stages of the red cell formation the antigen may not be mature. In an Rh negative anemic, six months multipara, with history of five previous abortions, we found her serum possessed an Rh agglutinin titer of 1:160. A sensitized, Rh negative mother may be further sensitized by every future Rh positive pregnancy. Should this mother's future fetus be Rh negative, there will be no difficulty due to Rh incompatibility since it is known that an Rh negative fetus cannot sensitize its negative mother. A transfusion of Rh positive blood following sensitization may produce severe or fatal reactions, regardless of the length of time after sensitization.

In the fetus a vicious cycle takes place due to the antigen-antibody union. When sufficient antibodies are absorbed from the mother, hemolysis occurs due to the presence of complement in the fetal circulation.

The extent of the incompatible damage to the fetus has a wide range of possibilities. The clinical evidence may be exhibited as spontaneous abortion, miscarriage, stillbirth, a monstrosity, erythroblastosis fetalis, icterohemorrhagica, anemia of the newborn, or there may be no damage. Erythroblastosis fetalis is the classical example that most clinicians are familiar with at present. Cook has suggested "that destruction of fetal blood cells by anti-Rh bodies in the blood of mothers may lead to serious injury to the fetal brain from anoxia" and that ". . . degenerative changes in cerebral structure may occur on a larger scale." Careful appraisal of this work should be made before too much significance can be placed in it.

Originally it was thought that the first pregnancy would not result in antibody production by the mother, or damage

to the fetus. It is now known that it may happen; generally, however, the first sensitization will not be injurious. It is possible that the injection of 10 to 40 cc. of incompatible blood to Rh negative babies may be enough to permanently sensitize them to the Rh factor.

## Sources and Preparation of Antisera

There are two known sources whereby anti-Rh serum may be obtained for use, namely, from experimental animals and from human beings. Experimental typing serum may be prepared by inoculation of Rhesus red cells into laboratory animals. Some animals are much better antibody producers than others. The guinea pig generally produces fairly good antiserum, while many rabbits do not respond to this antigen. Twenty-seven of the 30 guinea pigs inoculated at this laboratory (Eighth Service Command) produced good anti-Rh serum. Sheep, goats, and horses (Elliott) have been tried, but these animals are of little value for anti-Rh serum due to their production of extremely large amounts of species antibodies. The species antibodies are difficult to remove, and therefore, make the cost of production almost prohibitive in both time and money. Usually, large amounts of Rh negative human cells of all types are necessary for the removal of these species agglutinins. From experiments in this laboratory, it ordinarily requires about 10 volumes or more of washed, packed, Rh negative human cells, and repeated absorptions to completely absorb one volume of experimental guinea pig antiserum. If all undesirable agglutinins are not removed completely, false positive reactions are certain to occur. It is, however, almost impossible to over-absorb or remove Rh agglutinins when strictly Rh negative cells are used for absorption. The antiserum may contain hemolyzed material after repeated absorptions, yet some undesirable agglutinins remain. It is possible at times to dilute the antiserum to a point where the remaining undesirable agglutinins do not clump Rh negative cells. By the process of dilution, the Rh agglutinins are occasionally so weak that the antiserum is worthless. The removal of hemoglobin greatly improves the antiserum and this

can be accomplished by freezing and thawing. Some workers advocate only dilution to remove the effects of undesirable agglutinins, while other advocate only one absorption. Wiener (1942) states that "whether the absorbing blood is Rh positive or Rh negative seems to make little or no difference. . . ." We have found it requires O, A, and B, Rh negative cells for satisfactory absorption, also that Witebsky's A and B factor will not neutralize the undesirable agglutinins from our experimental antiserum. Experimental antiserum, when properly prepared, is useful primarily for screen tests. All negatives that are found with experimental antiserum must be retested with human antisera to detect the 2% Rh positives that the former fails to reveal.

The best source of anti-Rh typing serum is from patients who have been isoimmunized either by transfusion or pregnancy. By examining the serum of all patients suffering from transfusion reactions and all postpartum sera, whether or not there is immediate clinical evidence of Rh incompatibility, a laboratory has a good opportunity to supply itself with sufficient material for its own needs; and, furthermore, this may be the first source of information to the obstetrical service that the infant is erythroblastotic. Because of the uncertainty as to the length of time that Rh agglutinins will remain in a patient's serum, it is wise to examine postpartum sera within 24 hours after delivery. In some instances, as Wiener (1944) has shown, the agglutinins may disappear as early as thirty days postpartum, while Levine (1943) found agglutinins in one person longer than 1 year postpartum. Patients exhibiting reactions following transfusions may not have atypical agglutinins for as long as 10 to 15 days after a transfusion, and some may never have agglutinins, yet they may be sensitized, as demonstrated by the blocking test.

When anti-Rh agglutinins are discovered, it is rather easy to collect and prepare the serum. Secure as much blood from the patient as can be spared, allow the blood to clot, and remove the cells from the serum. The serum should be inactivated at 56° C. for 20 to 30 minutes to destroy complement. Natural agglutinins, such as alpha and beta in human

serum, are removed either by repeated absorption with Rh negative cells or by neutralization with Witebsky's A and B factor; the latter method is easier, time-saving, less expensive, and more satisfactory than the absorption process.

Inactivation may enhance the possibility of finding agglutinins in some sera, but may have no effect on others. A zone phenomenon may be marked in an occasional antisera which, if used in the undiluted state, will not agglutinate red cells. This unpredictable variability may be responsible for believing a serum contains no antibodies when actually they are present. Levine (1944) and Wiener (1944) have shown that some sera may show no agglutinins until a dilution of 1:4 or more is reached, while the maximum agglutination may occur at a very much higher dilution. In addition to inactivation and dilution of sera to bring out agglutination, we have found other peculiarities, in that some sera will exhibit agglutinins when diluted with certain buffers, and will not show agglutinins when diluted with normal saline.

## Classification of Cells and Value of Rh-Antisera

As previously stated, the Rh antisera can be subdivided into 5 groups. With the aid of these 5 groups of antisera, Wiener (1944) has classified 8 phenotypes of cells. The nomenclature of both antigen and antibody and the changing of terminologies by different authors has seriously handicapped progress. The following Table (I), containing old and new terminologies, may be of assistance in clarifying and dissipating existing confusion.

Table I

| Percentages of blood samples (White) agglutinated | Type of Serum (Classification) | |
|---|---|---|
| | *New* | *Old* |
| 35% | Anti Rh″ | Anti $Rh_0$ |
| 73% | Anti Rh′ | Anti $Rh_1$ |
| 84% | Anti $Rh_0$ | Anti Rh |
| 84.5% | Anti $Rh_0$″ | Anti Rh″ |
| 87% | Anti $Rh_0$′ | Anti Rh′ |

Wiener (1944) changed his classification of antisera from the old to the new, at the suggestion of Race and Taylor. As statistical data accumulates, the percentage of cells agglutinated by a given antiserum may increase or decrease, hence antiserum should not be named according to its percentage activity. For example, an 84% antiserum may eventually be changed to 85% or 82% after several thousand tests are made.

According to Table II, 7 phenotypes are antigenic and 1, the rh negative, is non-antigenic. These 8 phenotypes are genetically determined by 6 allelomorphic genes, $Rh_o'$, $Rh_o''$, Rh″, Rh′, $Rh_o$, and rh.

TABLE II

*The Various Rh Blood Types (After Wiener—Modified)*
*Science, 30 June 44, p. 532*

| Rh type phenotype cells) | Reactions with Rh Antisera | | | | |
|---|---|---|---|---|---|
| | 84% (Old Rh) New $Rh_o$ | 70–73% (Old $Rh_1$) New Rh′ | 35–37% (Old $Rh_2$) New Rh″ | 87% (Old Rh′) New $Rh_o'$ | 85% (Old Rh″) New $Rh_o''$ |
| rh (neg) .. | — | — | — | — | — |
| Rh′ ..... | — | + | — | + | — |
| Rh″ ..... | — | — | + | — | + |
| Rh′ Rh″ .. | — | + | + | + | + |
| $Rh_o$ ..... | + | — | — | + | + |
| $Rh_o'$ ..... | + | + | — | + | + |
| $Rh_o''$ ..... | + | — | + | + | + |
| $Rh_o'$ $Rh_o''$.. | + | + | + | + | + |

It is evident, therefore, from examination of Table II, that no single antiserum will agglutinate all Rh positive cells. The antiserum $Rh_o$ or the old Rh is now clearly differentiated from the term "Rh." This clarification of terminology will serve to avoid confusion. The $Rh_o$ antiserum is known as "standard Rh typing serum," and may be obtained from isoimmunized humans, or from experimental animals after immunizing with Rhesus cells. Generally, however, experimental antiserum is not very good and should be used with caution.

From the reactions of combination antisera (Table III) it may be seen that $Rh_o'$ antiserum is made up of or has the identical reactions obtained by using both $Rh_o$ and Rh′ antisera, while $Rh_o''$ antiserum gives the same results obtained

TABLE III

*Reactions of Combination Antisera*

| Cell Types | 87% $Rh_o + Rh' = Rh_o'$ | | | 85% $Rh_o + Rh'' = Rh_o''$ | | |
|---|---|---|---|---|---|---|
| rh (neg) ... | — | — | — | — | — | — |
| Rh' ..... | — | + | + | — | — | — |
| Rh'' ..... | — | — | — | — | + | + |
| Rh' Rh''..... | — | + | + | — | + | + |
| $Rh_o$ ..... | + | — | + | + | — | + |
| $Rh_o'$ ..... | + | + | + | + | — | + |
| $Rh_o'$ ..... | + | — | + | + | + | + |
| $Rh_o'$ $Rh_o''$ ... | + | + | + | + | + | + |

by using both $Rh_o$ and Rh'' antiserum. It is understandable then that if one has $Rh_o'$ and $Rh_o''$ antisera, one could readily determine whether any blood is Rh positive, or rh negative. It may also be seen why the Rh' or the Rh'' antisera cannot be used to good advantage in routine testing for Rh factors. It is interesting to note that Wiener (1944) has found more of the active antisera from human sources is of the $Rh_o'$ variety.

One of the difficulties in determining the proper cell classification (phenotype) of an individual is in securing an antiserum that does not have a complex make-up. For example, what is thought to be an Rh' antiserum actually may have weak $Rh_o$ agglutinins in it. The same idea holds true for the Rh'' antiserum; that is, it might also have anti-$Rh_o$ agglutinins, and thus may give a wrong classification of a person's cells until the $Rh_o$ agglutinins are removed. Antiserum containing two antibodies may be diluted to limit the reaction of the lesser antibody; however, this may not prove successful. For practical purposes of routine testing, only two antisera, the $Rh_o'$ and $Rh_o''$ actually are necessary, since the clinician is generally interested only in the positive or negative factors.

## TESTING PROCEDURES

*Routine Testing of Cells:*

1. To small test tubes about 75 mm. X 7 mm. add one drop of anti-Rh serum and one drop of approximately 2% suspen-

sion of the red blood corpuscles to be tested, by means of capillary pipettes.

2. Mix well and incubate at 37° C. for 30 minutes to 1 hour in a water bath or air incubator.

3. Carefully remove from the incubator and examine for the pattern of the cell sediment or "button," and macroscopic agglutination.

4. If macroscopic agglutination has not occurred, the tube should be placed under a microscope and the cells examined for microscopic agglutination. A hand lens of sufficient magnification may be used instead of the microscope.

5. Should no clumping be found, the tube should be gently centrifuged at 500 to 750 R.P.M. for 1 minute, and again examined for microscopic agglutination.

Clumping of cells indicate that they are Rh positive. No clumping indicates that the cells are Rh negative. By examining the cell sediment or "button" (No. 3 above) it sometimes is possible to differentiate positive or negative specimens. The positive "buttons" may be large and loose with irregular edges as compared to the small, compact, round, negative "buttons." It is known that all positive sediments will not form the above described positive "buttons," and further, a thickening or flattening of the bottom of the tube may prevent negative cells from forming a typical negative "button."

Great care must be exercised in examining the suspension since this agglutination is fragile and may disperse very easily. A false negative report might be given if the tube is shaken or roughly handled. It is well to mention here that most red cell suspensions, in saline or citrate, should not be used for Rh typing after 24 hours, since the agglutinating ability appears to be lost in some cells when they are off the clot for more than 24 hours. When cells are left in the serum undiluted, or left in the clot, it may be possible to make an accurate test 2 or 3 weeks later, depending, of course, upon the amount of red cell deterioration. When shipping blood samples through the mail for Rh testing, the blood should be drawn with *dry*, sterile equipment and forwarded in the orig-

inal tube in which it was collected. Specimens withstand cross-continent shipment by air mail very well.

*Testing Serum for Rh Agglutinins:*

Three procedures are available which may be followed when testing an unknown serum.

(1) Neutralization Method: This usually is accomplished by adding 1 volume of Witebsky's A and B factor to 2 volumes of the inactivated serum and allowing the mixture to remain at room temperature for 1½ hours. At times the alpha and/or beta agglutinins may be high, and the further addition of Witebsky's A and B factor is required to completely neutralize the normal antibodies. After the serum is neutralized, it is tested against known Rh positive and negative cells regardless of the Landsteiner groups.

(2) Intergroup Method: When using this method it is necessary to know the Landsteiner blood group from which the unknown serum came. Use several Rh positive and negative specimens of red cell suspensions of the same group to complete the test, for example, O serum against O cells, etc. Incompatibility of cells and serum of the same Landsteiner group is indicative of an atypical agglutinin, which may be found to be an Rh agglutinin by further investigation.

(3) Absorption Method: By using several specimens of Rh negative A and B cells, alpha and beta agglutinins may be absorbed from the unknown serum without much sacrifice of Rh agglutinins. Absorption is accomplished by adding the washed, packed cells to the serum, allowing the mixture to stand at room temperature, then removing the serum from the cells by centrifugation. Variations are many as to quantity of cells used, length of time of contact between cells and number of absorptions necessary before a serum is freed of alpha and beta agglutinins. Landsteiner and Wiener suggest a method of absorption for experimental serum which may be applied to human serum. They suggested that the serum (inactivated, if fresh) may be diluted 1:4 or 1:10 with normal saline and absorbed for one hour at room temperature with one-tenth volume of blood sediment. The absorbed serum

may be tested against any Rh positive and negative cells regardless of Landsteiner groups.

Further procedures are those described under "routine testing of cells." The interpretation of the results after testing the unknown serum are as follows: Should agglutination occur in a number of the positive cell specimens and not in the negative cells pecimens, it may be quite possible that the unknown serum contains Rh agglutinins. Clumping of negative cell suspensions and some of the positive cell suspensions may mean that the serum is not completely freed of alpha and beta agglutinins (by methods 1 and 3); that an error has been made in Landsteiner grouping (in method 2), or that the serum may contain the "Hr" factor. When clumping occurs in neither the positive nor negative cells, the serum contains no demonstrable antibody (Rh or "Hr"), but it may contain blocking antibodies.

The absorption procedure may not be advisable when testing an unknown serum from an Rh positive patient since absorption with Rh negative cells may remove the "Hr" factor, and absorption with Rh positive cells may remove the Rh factor. Thus the absorption procedure appears to be valuble for absorbing the serum of Rh negative patients, when neutralization or intergroup reactions cannot be used for preliminary testing.

*Blocking Test:*

Wiener (1944) has attempted to perfect a desensitizing method, but as yet it has not been published in the current literature as being successful. As a result of these studies Wiener (1944) has developed a technic known as the "blocking test," which has considerable merit. The purpose of the test is to detect those who are sensitized to the Rh factor but who do not have demonstrable agglutinins in their serum. Sensitized persons may have intra-group hemolytic transfusion reactions, or some of their babies may show effects of incompatibilities. It is well known that precipitation and agglutination tests will not always demonstrate sensitization. The "blocking test" is a good example of a new test to demon-

strate sensitization. The procedure given by Wiener (1944) is as follows: "One drop of a 2% suspension of Rh positive cells and a drop of the patient's serum are mixed in a small tube and allowed to react in a water bath at 38° C. for 30 to 60 minutes. Then a drop of a suitable dilution of an active anti-Rh serum is added, and after an additional incubation period of 30 to 60 minutes (38° C.), the reaction is read. If blocking antibodies are present, no agglutination will occur, or the clumping will be markedly weakened." We found that blocking antibodies were present in one mother at the time of delivery of an erythroblastotic infant. Wiener reported that about three weeks postpartum one mother developed the blocking antibodies with a titer of 1:2 to 1:4, and at that time almost all the anti-Rh agglutinins had disappeared from her serum. He attributes this to the serum's containing both agglutinating and blocking antibodies at the time of delivery, and that the agglutinating antibodies disappeared more rapidly than the blocking antibodies.

*"Hr" Test:*

When using the "Hr" serum, the procedure of the test is the same as described in *"Routine Testing of Cells."* By use of "Hr" antiserum the necessity of typing all of the subject's family and many relatives to determine whether one of them is heterozygous or homozygous is precluded. It is important to know if a father is heterozygous or homozygous when advising mates whether or not to attempt future pregnancies after some of their offspring have died as the result of Rh incompatibility. When the mother is Rh negative, homozygous (rhrh), and the father is Rh positive, heterozygous (Rhrh), there is a chance for a safe delivery since about 50% of the children will be Rh negative. However, if the father is homozygous (RhRh) it is wise to advise aganist a future pregnancy, since all offspring from such matings will be Rh positive. Records seem to indicate that this is sound advice. Wiener (1944) indicates that most anti-Hr sera are of low potency,

but both Levine (1942) and Davidsohn (quoted by Wiener, 1944) discovered antisera of diagnostic potency. The following results with a similar antiserum (St) were obtained by Race, Taylor, Chappell and McFarlane.

TABLE IV

| Genes (cells) | Antisera | | | | | |
|---|---|---|---|---|---|---|
| | Rh | St | $Rh_2$ | $Rh_1$ | Rh′ | Rh″ |
| $Rh_1$ | + | — | — | + | + | + |
| $Rh_2$ | + | + | + | — | + | + |
| $Rh_3$ | + | + | — | — | + | + |
| Rh′ | — | — | — | + | + | — |
| Rh″ | — | + | + | — | — | + |
| rh (neg) | — | + | — | — | — | — |
| Rhy | ? | — | + | ? | | |

From inspection of the results of Race, Taylor *et al.*, it is observed that the Rh negative cells give a positive reaction with "St" (or "Hr") serum. It is also known that all Rh negative and heterozygous (Rhrh) positive cells will clump with this serum, but about half of the homozygous (RhRh) positive cells will not clump. Those that do not clump have genotypes $Rh_1Rh_1$, $Rh_1Rh'$, $Rh'Rh'$.

"Hr" serum is very valuable in medico-legal work. In disputed parentage cases it may be the key to the identification of the suspected father or it may prove a man could not possibly be the father of a certain child. In research problems it is extremely valuable also for classification of cells.

## SOME PRACTICAL APPLICATIONS

For many years it has been an accepted practice to use the husband as a donor when his mate or offspring was in need of a transfusion, provided that he was of a compatible group. As a practical application of the knowledge of Rh factors, it is inadvisable, in most instances, to use the father's blood when transfusing mother or offspring, especially when there is a difference in Rh characteristics of the parents. A hemolytic reaction may occur if the father's blood is used, because the antibodies produced by the mother may be in her serum or

in the baby's serum. The addition of the father's identical antigen (his red cells) will aggravate the condition, and may prove fatal.

It also has been the practice to transfuse an anemic newborn with its mother's blood. Should the mother have antibodies against her child's cells, a bad situation is made worse. Some clinicians have successfully given transfusions to Rh positive newborn, after washing the mother's Rh negative blood free of serum to remove antibodies and resuspending the cells in normal saline. The procedure is acceptable for use in emergencies until other Rh negative donors are found.

The fate of Rh antibodies in the newborn is not known. It is known that after varying lengths of time the Rh agglutinins disappear from the infant's blood, which leads to the belief that these agglutinins may be eliminated. Thus, Rh positive infants, after elimination of antibodies, may be transfused with Rh positive compatible cells.

When a non-sensitized individual is Rh negative and receives multiple transfusions within a short period of time, immediate reactions are not due to differences in Rh factors, but are due to other causes. If the subject has been sensitized previously to the Rh factor, the immediate reaction following transfusions may be due to one of the Rh antigens. Antibodies may appear seven to ten days after transfusions.

Difficulties are encountered in establishing the Rh factor following transfusion, particularly if the patient is Rh negative and receives Rh positive blood. It has been shown by Landsteiner, Levine and Janes that transfused blood cells could be detected in the recipient's circulation for as long as 14 weeks. To obviate this difficulty, the Rh factor should be determined before transfusion, or at least pre-transfusion specimens of whole blood from the patient should be preserved for future use.

## Summary

The "Rh factor" is a term applied to a group of similar antigenic substances in certain red blood cells. At present the antigens have been found only in the erythrocytes of humans

and in certain of the Rhesus monkeys. They all appear to be much alike, but are not identical, and each variant may produce a reaction in both transfusions and pregnancies. These reactions are due to isoimmunization or sensitization by the various Rh antigens, and follow either transfusions or pregnancies, or a combination of both.

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# QUANTITY OF MENSTRUAL FLOW*

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## Quantity of Menstrual Flow

Hippocrates and investigators since his time, have attempted to determine the quantity of material lost in normal menstruation. Clinicians, on the other hand, have been interested in practical figures to aid them in studying patients with menstrual disorders, sterility, hypochromic anemia and various other conditions. The present study surveys work of previous investigators and presents additional information obtained from studies in Galveston, Texas, with a view toward establishment of a simple, accurate and clinically practicable standard for measurement of menstrual flow.

## Survey of the Literature

Methods used in the past to determine menstrual volume vary from collection of the material in a vaginal cup and direct measurement of its volume to the highly precise procedure of quantitative analysis of the material collected on cellulo-cotton pads for iron and calculating the weight or volume of blood lost on the basis of the subject's peripheral hemoglobin. There is no consistency in reports. Values are given ranging from 1 to 20 oz. (29.5 to 590 cc.) and from 20 to 500 Gm. While some investigators have based their studies on the iron lost, others have considered the total gross volume or weight of the material, including epithelial debris, uterine secretions, mucus, etc. Many figures are based on the study of only a few cases. These measure discharge for the whole bleeding phase, while some record that for only fractions of the period.

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*From the Department of Obstetrics and Gynecology, The University of Texas Medical Branch, Galveston, Texas. Received for publication May 30, 1945.

Table I summarizes these various reports. It is similar to that presented by Barer and Fowler (1936) but contains a few additional values.

TABLE I

*Figures from the Literature*

| Author | Loss on Menstruation |
|---|---|
| Anspach | 4–6 oz. |
| *Arens | 11.7–157.8 cc. |
| Astruc | 8–10 oz. |
| Barer & Fowler | 6.55–178.69 cc. |
| Baudelocque | 3–4 oz. |
| Crossen | 150–300 cc. |
| Das | 55–200 cc. |
| Eichmann | 2.61–61.25 cc. |
| Fitzgerald | 14–15 oz. |
| Freind | 10 oz. |
| Fraenkel | 30–50 Gm. |
| Fulkerson | 12–15 napkins. |
| Galen | 18 oz. |
| Gebhard | 90–240 Gm. |
| Gilbert | 120–240 Gm. |
| Gley | 200–500 Gm. |
| Gorter | Not over 6 oz. |
| von Haller | 6–12 oz. |
| Haen | 3–5 oz. |
| Hensen | 100–200 cc. |
| Hippocrates | 20 oz.: 600 Gm. |
| Hoppe-Seyler | 26–52 cc. |
| Howell | 100–200 cc. |
| *Jansen | 2–50 cc./24 hrs. |
| Kelly | 60–240 cc. |
| Lahille | 20–80 Gm. |
| *Leverton & Roberts | 11.13–22.84 mg. Fe. |
| Linnaecus | Very little. |
| Magandie | May be several lbs. |
| Mayer | 210 Gm. |
| Meigs | 1–20 oz. |
| Novak | 2–8 oz. |
| *Ohlson & Daum | 18.16–41.90 mg. Fe. |
| Penrose | 2–9 oz. |
| Pasta | 90–240 cc. |
| Penard & Abelin | 100–200 Gm. |
| Prussak | 100–150 Gm. |
| *Smellie & Dobson | 4 oz. |
| Viault & Jolyet | 100–200 Gm. |

All authors except those indicated by (*) are quoted by Barer and Fowler (1936).

Lahille's work deserves special mention for its precise analyses, although only 7 cases were studied. Pointing out that the values given by Hippocrates and Galen were too high, he concluded that 25 per cent of women do not lose over 20 Gm. of blood, 50 per cent lose from 50 to 55 Gm., and 25 per cent lose 60 Gm. or more. He opined that a tendency to abnormal conditions is suggested when the blood loss is over 80 Gm.

Sister M. Alcuin Arens, in a study of blood lost during menstruation in students between the ages of 15 and 23 years, has recorded blood volumes for 60 menstrual periods. Values range from 11.7 to 158 cc. with a mean of 58.1 cc. Rather than to determine blood losses per se, she attempted to correlate blood loss with the individual's blood volume. No such correlation was demonstrated.

Hoppe-Seyler based his figures on the study of only 15 women, 11 of whom he considered pathologic. Blood loss in the 4 normal women ranged from 26 to 52 cc.

Barer and Fowler have done the most extensive and complete work in this field. Their procedure has been to collect the menses either on cellulo-cotton pads or in vaginal cups and analyze for iron. From this, the volume of blood lost was calculated, considering menstrual and peripheral blood to contain equivalent amounts of hemoglobin. Barer, Fowler and Baldridge (1935) in a series of 50 cases found that the iron loss varied from 3.84 to 78.4 mg. per period, representing a blood loss of 9.39 to 207.28 cc. with a mean of 36.7 cc. They concluded that the greater figure was above the range of normal since about 2.8 mg. of iron would have to be retained daily to restore that lost from menstruation. Results of iron balance studies in connection with which these menstrual blood loss determinations were made suggested that such a high iron retention would be distinctly unusual with average dietary iron intake. This, they pointed out, might well explain the development of certain cases of idiopathic hypochromic anemia.

In 1936, Fowler and Barer studied 100 cases. In this group the blood loss varied from 6.55 to 178.69 cc. with a mean of 50.55 cc. and a standard deviation of 25.73 cc. In the course of this study it was found that there was no correlation between

the age of the patient and the amount of blood lost, nor between the blood lost and the blood hemoglobin therein. The mean loss in the 76 unmarried women studied was 52.96 cc., whereas that in the 24 married women was 42.91 cc. Bleeding was more profuse in parous (13 cases, mean loss 48.18 cc.) than in nulliparous women (11 cases, mean loss 36.68 cc.). In 3 groups of sisters included in the study, no familial tendency was detected in menses. Although in general the blood loss varied with the length of the menstrual period, there were marked individual variations as in one subject who had a loss of 109 cc. in three days and in another in whom only 31.07 cc. were lost in seven days. There was also marked individual variation in the number of napkins used, depending as much or more on fastidiousness and economic status than upon the quantity of flow. The subject's statement that her menses were normal could not be relied upon, as she had no standard of comparison other than the uniformity of her own menses. Neither those losing exceptionally small amounts nor those losing very large amounts of blood were impressed by such losses. It was observed that in some instances the variation in blood lost from month to month was only slight, while in others, it was very significant. It was concluded that although one is not justified in setting definite limits on the blood loss in normal menstruation, it is significant that 50 per cent of the women in this series lost between 23.21 and 68.3 cc., and that great variations from this range can hardly be considered normal.

In 1938, blood losses were observed to range from 94.02 to 922.45 cc. in 18 women with menorrhagia (Barer and Fowler). It was of particular interest that the patient who lost the 922.45 cc. of blood stated that her menses were not profuse.

The reports of Arctic explorers that women of the far north menstruate very little are substantiated by Linnaeus in his "Flora Laponica" in which he says that these inhabitants of the frozen north, such as the Samoyedes, bleed very slightly and only in the summer months, whereas the women of Greenland have scarcely any bleeding.

## II. Present Investigation

The chief aim of the present study was to ascertain the variations in the quantity of material lost by normal menstruation, employing a standard method. By extending the project to cover several menstrual periods for each participant, it was hoped to note period variations in the individual case. So far as can be determined from the foregoing review of the literature, no similar studies have previously been undertaken on women in this geographic area; therefore, comparison of the following results with those obtained by workers elsewhere might be of interest.

### Approach

A representative group of 96 unmarried volunteers between the ages of 17 and 35 were readily available in the John Sealy College of Nursing. These subjects were organized through the Department of Obstetrics and Gynecology and the College of Nursing. Each woman was designated only by a number, thus preserving anonymity. Weighed boxes of sanitary napkins and weighed, opaque, air-tight jars of 3 liter capacity were provided in the nurses' dormitories, with detailed instructions as to procedure: at the onset of bleeding, a jar and as many boxes of sanitary napkins as might be required were returned with the jar containing used pads, accompanied by the participant's number and information relevant to the period. Calculations were made by subtracting the weight of materials issued from that of materials returned.

At the outset, information was obtained from each subject, as in Form A, while Form B was returned at each period.

PERMANENT FILE

Number..... Age..... Weight..... Height.....inches.

Menstrual History:
Menarcheat age of..... Regular ( ). Irregular ( ). Interval.....
Duration of flow..... Clots—Yes ( ). No ( ). Number of pads normally used..... Date....., 1944. Date of last period....., 1944.

Average temperament: Easy going ( ), high strug ( ), lazy ( ), industrious ( ), depressed ( ), irritable ( ).

Menstrual temperament: Easy going ( ), high strung ( ), lazy ( ), industrious ( ), depressed ( ), irritable ( ).

Dysmenorrhea: Always ( ), sometimes ( ), never ( ). Other pelvic pain ( ), Mittelschmerz ( ).

MENSTRUAL HISTORY

Number.....

Date flow began..... Morning ( ), afternoon ( ), night ( ).
Date flow ended..... Morning ( ), afternoon ( ), night ( ).
Number of pads used..... Clots—Yes ( ). No ( ).

Type and severity of dysmenorrhea, if present:
Aching ( ), lancinating ( ), (cramping ( ), mild ( ), moderate ( ), severe ( ). Do ( ), do not ( ), require bed rest.

Temperament during menstruation: Easy going ( ), lazy ( ), depressed ( ), high strung ( ), irritable ( ), industrious ( ).

Pain noticed before ( ), during ( ), after ( ) flow begins.
Location .....
Radiates to.....
Accentuated by: Standing ( ), movement ( ), defacation ( ), urination ( ), others (specify).....

Medication before ( ), during ( ), after ( ) menstruation.
Type of medicine (name).....

Mass of flow.....gms. (recorded by technician).

Hence, all essential information and data were constantly on file. Further questions as to subjective abnormalities, plus other subjective aspects not pertinent to this study, were included on a third form, not shown.

The completed study covered a period of six months, from March through August 1944, and a total of 319 bleeding phases of the menstrual cycle in 89 women.

## Findings

The range in age of the subjects studied was from 17 to 35, with an average of 20. The age of menarche was from 6 to 16, averaging 12.6. Dysmenorrhea occurred in 60.5 per cent, with time relationships shown in Table 2. It is interesting to

Table II

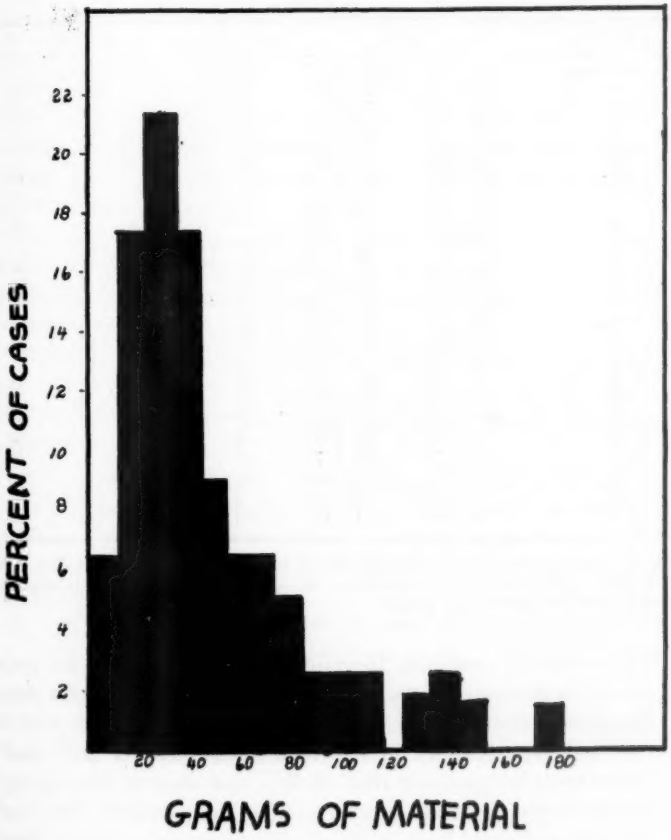
*Incidence of Dysmenorrhea*
*89 Cases*

| | | Per Cent |
|---|---|---|
| No Dysmenorrhea | | 14.6 |
| No Report | | 24.7 |
| Dysmenorrhea Reported— | | |
| Before Bleeding Phase | 13.5 | |
| During Bleeding Phase | 12.4 | |
| After Bleeding Phase | 6.7 | |
| Before and During | 18.0 | |
| Before, During, and After | 10.0 | |
| During and After | 0.0 | |
| Total Reporting Dysmenorrhea | | 60.6 |

note that no subject reported the occurrence of pain during and after bleeding only. There was no correlation between the severity of dysmenorrhea and the amount of flow, or the age, or any combination of these three factors.

*Mass of Material Lost with Menstruation* varied over a wide range in 82 women, from 5 to 156 Gm., with a mean of 48.5 and a standard deviation of 34.4 (figure 1). Some of the ex-

FIG. 1.



treme cases probably should be considered abnormal, but complete clinical correlation was not possible under the conditions of the experiment. It should be mentioned that in most of the extreme cases, the subjects *considered themselves normal.*

Table 3 presents findings in 24 subjects on whom records were compiled over 4 or more periods. Duration of the flow

TABLE III

*Period Variations in a Given Individual*

*24 Cases*

| Case | Dur. | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| 2 | 5 days | 152 (18) | 179 (23) | 113 (16) | 131 (20) | |
| 9 | 4 | 20 ( 8) | 22 (10) | 27 (12) | 21 (10) | 24 ( 9) |
| 19 | 5 | 53 (12) | 73 (18) | 90 (17) | 91 (21) | |
| 22 | 5 | 12 ( 4) | 14 ( 7) | 31 (11) | 26 (12) | |
| 33 | 3 | 41 ( 8) | 34 ( 8) | 28 ( 8) | 61 (11) | |
| 34 | 5 | 46 (10) | 47 (12) | 58 (12) | 43 (12) | 48 (12) |
| 35 | 6 | 26 (12) | 39 ( 7) | 47 (12) | 48 (11) | |
| 45 | 4 | 63 (11) | 72 (11) | 70 (11) | 67 (15) | |
| 49 | 4 | 23 ( 8) | 26 ( 6) | 38 ( 8) | 41 ( 8) | 22 ( 4) |
| 53 | 5 | 84 (12) | 32 (10) | 37 (11) | 33 (12) | |
| 56 | 3 | 28 ( 6) | 25 ( 5) | 11 (10) | 33 ( 8) | 32 ( 7) |
| 59 | 3 | 31 ( 7) | 45 ( 7) | 48 ( 9) | 33 ( 6) | 59 (10) |
| 67 | 4 | 122 ( 9) | 84 ( 9) | 78 ( 8) | 68 ( 8) | 56 ( 8) |
| 68 | 3 | 27 (11) | 33 ( 8) | 40 ( 9) | 25 ( 8) | 34 ( 8) |
| 70 | 4 | 20 (13) | 21 (12) | 26 (12) | 11 (10) | 12 ( 9) |
| 72 | 4 | 33 ( 9) | 7 (10) | 12 (10) | 29 (11) | |
| 73 | 3 | 8 ( 6) | 22 ( 7) | 10 ( 7) | 18 (11) | 13 ( 8) |
| 78 | 4 | 64 ( 6) | 66 ( 8) | 28 ( 8) | 72 ( 8) | |
| 82 | 5 | 101 (23) | 120 (29) | 159 (30) | 131 (27) | 160 (22) |
| 83 | 4 | 9 ( 7) | 29 (10) | 4 ( 5) | 18 ( 9) | 20 ( 6) |
| 88 | 4 | 12 ( 7) | 18 ( 7) | 24 ( 9) | 21 ( 9) | 53 (11) |
| 90 | 4 | 37 (14) | 32 (10) | 32 (12) | 37 (10) | 46 (11) |
| 92 | 2 | 4 ( 6) | 10 ( 3) | 2 ( 2) | 8 ( 5) | |
| 95 | 4 | 53 (12) | 61 (12) | 65 (11) | 59 (12) | 54 (12) |

The figures in columns No. 1 through No. 5 represent the menstrual flow in grams for any one period. The figures in parentheses are the number of sanitary napkins used by the individual for that particular period.

The periods represented are successive but not all consecutive.

was relatively constant, therefore, only the average for each person is shown. Mass of flow, on the other hand, shows some fluctuation from month to month in a given subject and is reflected very roughly in the variable number of pads used. Correlation between duration of flow and mass of flow is negligible *except in extreme cases,* e.g., cases 2 and 92. But case 35, with a slightly long duration, shows less than average flow.

Table 4 shows a comparison between duration and quantity of flow, demonstrating a direct relationship in a large series;

TABLE IV

*Relationship Between Duration of Period and Quantity of Flow*
*77 Cases*

| Duration of Period (Days) | Per cent of Cases | Menstrual Flow in Grams | |
|---|---|---|---|
| | | Variation | Average |
| 1 | 1.3 | 10 | 10 |
| 2 | 1.3 | 6 | 6 |
| 3 | 15.6 | 15– 43 | 28 |
| 4 | 28.6 | 5–106 | 42 |
| 5 | 36.3 | 21–145 | 60 |
| 6 | 13.0 | 12– 91 | 42 |
| 7 | 3.9 | 29–165 | 95 |

however, a negligible correlation is noted in individual cases. Duration was observed to vary over a range of one to seven days with mean of 4.4.

As has been noted by previous workers (Barer and Fowler, 1936), the number of pads used is an individual function. The subjects in our study may be considered as intelligent, relatively fastidious and were furnished pads at no obligation to them.

Clots were reported by 48 per cent of the women, 36 per cent reported no clots, while 16 per cent did not reply on this point. No correlation was noted between the occurrence of clots and dysmenorrhea.

In 84 patients reporting, bleeding began in the morning, in 58 per cent; in the afternoon in 19 per cent, and during the night in 22 per cent. The time of onset in successive periods in the individual case was fairly constant, although there were significant variations.

## DISCUSSION

Numerous difficulties, mechanical and otherwise, contributed sources of error which are worthy of mention. These include losses from, or in addition to, the menstrual material per se: through such factors as urination (shown to be negligible by Barer and Fowler, 1936), loss prior to donning pad, bathing, feces on pad and evaporation. The latter may well be an

important factor in loss of weight, especially while wearing the pad, but since it cannot be controlled without elaborate maneuvers and since it occurs to a more or less constant degree so long as a procedure standard in other more readily controllable respects is followed, it can, for clinical purposes, be disregarded.

Other more flagrant sources of error include a partial lack of understanding and/or coöperation on the part of the subjects (responsible for the invalidation of more data than all other factors combined), foreign bodies in jars (bath salts, deodorant powder, papers), and a lack of clinical correlation due to the preservation of anonymity and the wholly voluntary nature of the project.

No conclusions have been drawn as to possible seasonal variations in flow, as the study extended over too short a period for adequate comparison along these lines. Nor were any detailed statistical analyses attempted in view of the relatively small group represented. No chemical determinations were resorted to, as *universal clinical application* was considered the prime purpose of the study. It may be pointed out, however, that figure I corresponds strikingly with findings on hemoglobin iron in menstrual fluid noted by Barer and Fowler, 1936.

It is hoped that additional data regarding conditioning and emotional factors in menstruation may be presented at an early date.

## Conclusions

The variation in quantity (i.e., mass) of material lost at normal menstruation is great, in our subjects ranging from 2 to 165 Gm. In our series, the mean variation was 48.5, and the standard deviation 31.4.

Almost two-thirds of the subjects had dysmenorrhea, while one-half reported clots. Duration of flow is constant and the mass of flow is somewhat variable for a given subject. The number of pads used is a rough guide to the menstrual flow. Little or no correlation was shown between dysmenorrhea, quantity and age; between clots and dysmenorrhea. A relation between mass and iron loss is noted.

Numerous sources of error exist in this study, but were for the most part ignored, being either slight or unavoidable. Full coöperation by subjects was not realized.

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# AVIATION AND THE DOCTOR*

EUGEN G. REINARTZ†

In the early months of 1942, I had the privilege of addressing the faculty and student body of this school. This was a memorable occasion for me, so it was with much pleasure that I accepted the invitation of Dr. Gregory to be present here this afternoon to deliver the Alpha Omega Alpha lecture, choosing as my subject, "*Aviation and the Doctor.*"

Since the major progress in aviation has taken place in the military services, so also has the progress of medicine in connection with flying had its greatest stimulus and development in these services and in the Army primarily. However, the interest of the doctor in flying has been evidenced since the imaginings of man began to actually attempt to create heavier-than-air flight, and at a time when the medical man was an anatomist and not the well rounded professional man he is today and as he is so well and ably trained in this school.

Flying is foreign to an individual's biological development and not at all in keeping with his normal terrestrial experiences, so it creates stresses and strains that call for a rapid adaptation to numerous situations. These may be adequately handled; however, they may also create difficulties dependent on the degree to which the individual is physically and psychically unadapted for such tasks. Throughout the history of aviation, such difficulties as developed in flying personnel fell and still fall in the medical field. This, then, constitutes the reason for the close linkage of medicine with flying since its inception. I have been wont to say "Medicine and aviation are indissolubly wedded and may never be divorced."

Many people, through the ages, have watched birds in their unerring flight, never misjudging distance and avoiding all ob-

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stacles. The instincts, the precision of formation and the certainty of reaching their destination are the result of using equipment given birds by a Creator that we who would emulate them might well possess. Here there is no problem by reason of possession of these endowments.

Since man, throughout the years, has had difficulty of adaptation to this new sphere, one must begin with the earliest phase of flying going back to the year 1500 when Leonardo da Vinci, the great anatomist, became deeply interested in aerial flight. His prescience in these matters is indicated by the treatises he wrote on the subject; the models he developed that were able to lift themselves into the air without the employment of light gases and his planning of the first helicopter—the vertical lift type of aircraft.

Very little is of record from these early beginnings until the time when the Montgolfier brothers caused the first balloon flight to be made at Annonay, France, in 1783. This was made without human passengers; however, since the interest of these brothers was primarily in the physiological field and they wished to find out the effect of flight on living creatures, they sent aloft sheep and fowl to an altitude of several hundred feet. History records their gratification, wonderment and astonishment that these living things showed no baneful effects as a result of their aerial ascent.

As a result of those findings and during the same year, the first human aerial voyage was made in a balloon by Pilatre de Rosier, who ascended to approximately 3000 feet. Subsequently, during December of 1783, a balloon ascent was made carrying a human being to 10,500 feet. The record of this flight chronicled for the first time physical discomfort suffered by these individuals as they reached an altitude. The balloonist complained of the severe cold and of pain in the right ear and jaw, a finding which even to the present is producing many days lost from duty and constitutes one of the principal problems in our otolaryngological research at this time.

In 1784, one of those intrepid souls, who like General Billy Mitchell, develop and emerge from time to time from the population, made his appearance and at his own expense took a

balloon flight with Pierre Blanchard. This individual was Dr. John Jeffries, who, although an American, had settled in England, and while a keen meteorologist was the first medical man to study aviation medicine.

In January 1785, Jeffries made the memorable first flight across the English Channel. During this aerial voyage he jettisoned almost all of the equipment carried, both personal and scientific. He, however, made recordings of barometric pressure, temperature, took along bottles of water so as to obtain samples of air and described his personal reactions in detail.

It was during this epochal flight too that Jeffries became the bearer of the first air mail letter, having carried it from London to France where it was delivered to Benjamin Franklin.

For this unprecedented flight, Jeffries was feted in France and England and was made Warden of Cinque Ports, an honor granted only to specially distinguished men. The present holder of this honor is the British Prime Minister, Mr. Winston Churchill. The Institute of the Aeronautical Sciences has recognized the outstanding feat and scientific recording of these flights by the John Jeffries award that is presented annually to those who have been outstanding pioneers in aviation medicine. The speaker has been the recipient of this award.

The first handbook on the subject of aeronautics was published in 1786, and the author, though a lay person, recommended balloon ascents for convalescence stating of individuals who took balloon flights "their spirits were raised by the purity of the air and rest in a cheerful composure. In an ascent all worries and disturbances disappear as if by magic." It was further his opinion that this salubrity was due to a change from "hot putrid and impure to cold pure air impregnated with invigorating aerial acid." Ballooning was also recommended as a means of promoting longevity. It was further claimed that tuberculosis, neuralgia and many other diseases might be cured by balloon ascents. Enthusiasts of this new art also thought it offered wonderful therapeutic possibilities and this, at least in the case of deafness, was believed to be true by many until the very recent past.

In the year 1800, one finds the first scientific record of altitude effect on the human body. The condition was described as "balloon sickness" and stress was laid on the physiological effects of rising to an altitude.

During the 19th century, much thought was expended on the development of gliders and in 1840, George Peacock of England, demonstrated the first man lifting kite, which, possibly unknowingly, demonstrated for the first time the principle that air moving against an inclined plane surface could provide sufficient lifting force to sustain the weight of an individual.

From that period to the end of the century might well be called the period of gliders, for it was during this time that Lilienthal in Germany, Montgomery, Chanute and Wrights in America; Pilcher in England and LeBris in France were devoting their efforts to the evolving of a more specific knowledge concerning the lifting power of various wing forms.

During this period, namely the time intervening between the balloon and heavier-than-air flights, but one publication of medical note was produced. This was the outstanding book of Paul Bert "La Pression Barometrique" written in the year 1878. The latter half of this volume dealt entirely with decreased barometric pressures and other phases of anoxemia. The book lay dormant and unnoticed by research workers for a period of sixty five years, its importance being unrealized. It was not until the year before last, in 1943, that the translation of this book was first made and it now constitutes the standard text in matters relating to anoxia and the effects of decreased atmospheric pressures.

Some in this audience remember the momentous day in December 1903 when the Wright brothers made the first successful power driven flights in an airplane at Kitty Hawk, North Carolina. These were the first successful passenger carrying flights in a self-propelled heavier-than-air flying machine. The Wright brothers have therefore gone down in history as the first men to fly in a controlled plane.

Those here present who remember the first years of aviation will probably also remember the breath-taking articles that appeared in the public press with statements that this new

fangled gadget was an invention of the devil and those who participated would come to no good end; that this new contrivance defied all of the laws of God and man. There were those visionaries, intrepid souls who immediately envisioned and projected the potentialities and possibilities of this new contraption and who dreamed with Tennyson when he wrote as though inspired, in "Locksley Hall,"

> "For I dipped into the future, far as human eye could see,
> Saw the Vision of the world and all the wonder that would be;
> Saw the heavens fill with commerce, argosies of magic sails,
> Pilots of the purple twilight, dropping down with costly bales."

The first fatal airplane accident occurred in a military machine at Fort Meyer, Va., in September 1908, in which Lt. Thomas Selfridge, for whom Selfridge Field, Michigan is named, was killed and Orville Wright was severely injured. This focused medical attention on this new method of aerial transportation. A few years later, Cruchet and Moulinier published some scientific articles which were subsequently published in book form under the title, "Airsickness."

By reason of the public attitude toward this death defying development, very little medical interest was shown between the time of the first flights and the year 1911. Such medical interest as was present was rather spasmodic in character and confined principally to the physiology of altitude. No physical examination was required for military aviators, nor was there a physical examination required for civilian aviators. Furthermore, the general supervision of those who were detailed to flying was practically non-existent, the attitude being that if an individual chose to take his life into his hands, that was his own matter.

In 1912, the War Department of the United States published the first instructions concerning the physical requirement to be met by those who wished to be candidates for and be trained as flyers in the Army. During the latter part of the same year,

the Bureau of Medicine and Surgery of the Navy Department issued its regulations concerning the standards of physical examination for naval aviation duty.

In rapid succession, Germany, Italy and Great Britain developed physical examinations for selection of flying personnel. It was during the years 1914 to 1915 that Great Britain proved beyond reasonable doubt that these physical examinations were necessary. During the first year, the British found that an overwhelming percentage of casualties was due to some defect of the pilots themselves for whatever reason. This is now aptly called "cockpit failure." The finding sharply focused medical thought on the physical and mental aspects of flying and was responsible for the decided change in the nature of the examination that was subsequently required.

To the late Brig. Gen. Theodore C. Lyster must be given credit for the appreciation of the importance of high temperamental and physical qualifications necessary for those who would engage in flying. He began his work in connection with the development of physical standards for the United States Army in July 1914.

In fixing the scope of the examinations and in a search for other similar standards to be followed, particularly as regards the eyes and ears, a search was made for such regulations as might be in force in foreign Armies. If there was any such regulation, none was forthcoming and reliance was placed on a text on the subject of "Physiology." There were no precedents in these matters.

It was believed at first that the standards set were too high and the head of the Aviation Section of the Signal Corps, as the Army Air Forces then were known, requested that these be lowered and these were modified as more experience was gained.

The knowledge gained by our Allies was subsequently placed at the disposal of the United States Government at the time of its entry into the World War I. When war was declared on the Axis powers in 1917, the Air Service of the United States consisted of 65 officers and 1120 enlisted men. These increased within a year to 14,200 officers and 124,700 enlisted men. Many special problems naturally arose in consequence of the fact that

work in the air, in war, was the primary object of the Air Service, and the Medical Department had no precedent by which to be guided, having had no previous practical experience of its own.

American aviation medicine really had its beginning and an era of a new type of medicine was begun when the then Major Lyster recommended that an officer of the Medical Corps be placed in charge of the physical examinations of all applicants for duty with the Aviation Section, Signal Reserve Corps.

It is stated that in 1917, stress was laid entirely upon the selection of those who would become flyers as contrasted with the present method where selection, maintenance and rehabilitation go hand in hand.

It was at this time in 1917, that the organization of the Medical Research Board took place. The powers delegated to this Board were as follows. The Board shall have discretionary powers (1) to investigate all conditions which affect the efficiency of pilots; (2) to institute and carry out at flying schools or elsewhere, such experiments and tests as will determine the ability of pilots to fly in high altitudes; (3) to act as a standing medical board for the consideration of all matters relating to physical fitness of pilots. The Board immediately started functioning and as subsequent matters proved, was wiser than its generation, for there is no major problem facing the doctor in aviation today, that was not envisioned, at least in part, and worked upon by those eminent individuals constituting the Medical Research Board.

The Research Board in due time organized a Medical Research Laboratory. This began functioning on January 19, 1918 as a central medical research laboratory at Hazelhurst Field, Mineola, Long Island. This laboratory was the progenitor of the School of Aviation Medicine, located since 1931 at Randolph Field, Texas.

During World War I and subsequent thereto for a few years, much interest was shown in all of the medical problems associated with aviation. Research was conducted along numerous lines. High altitude tolerances were determined by the use of the Henderson-Pierce rebreather and one small low

pressure chamber, and much was done to place the physical examination for flying on a scientific basis.

Subsequent to this and with the reduction of the Armed Forces, interest in aviation lagged and the Air Service was relegated into a position known as "the stepchild of the Army." With many of the medical officers who had been assigned to Air Corps duty returning to their peaceful pursuits, the numbers of those assigned to duty with flying also became pitifully and woefully small. Due to retrenchment on the part of the Federal Government and the "back to normalcy" program, funds were not available to continue the research in matters of aviation that had been so auspiciously begun.

Since its inception and until 1940, the School for Flight Surgeons being the only one of its kind, trained medical officers of both the Army and the Navy, the first of the Naval Flight Surgeons graduating in the spring of 1922. It was also during this year that the name of the School for Flight Surgeons was changed to that which it now carries, namely, the School of Aviation Medicine.

In 1926, one of the most notable developments in connection with flying took place and its development in its entirety was the result of medical research by Lt. Col. David A. Meyer, M.C., assisted by Col. William C. Ocker, A. C. In the opinion of the speaker, this, next to flying itself, is the most important development that has occurred in connection with flying, and was the basis for the tremendous upswing in aviation; of the extension of flying from short flights of that day to the long and extended cross-country, transoceanic flights and tremendous bombing missions that are now the rule. These two officers firmly established the basic principles from the human standpoint on which the art of instrument flying was founded, namely, the interpretation of the illusions originating in the equilibratory mechanism of the internal ear. They are indeed known as the "fathers of blind flying." The principles enunciated by them brought pointedly to attention the numerous deaths occurring in cross-country flights when external objective reference was impossible and these illusions beset the pilot as in clouds, fog, storm, snow and moonless nights.

The first dramatic demonstration of the application of the enunciated principles in connection with instrument flying was given by the Pan American Airways. This company flew its ships from Brownsville, Texas, to Mexico City. Over a large portion of this route, conditions prevailed that made so-called "contact flying" impossible. Prior to the enunciation of the principles of instrument flying, numerous flights by this company could not be completed as the pilots had to land because of weather. Subsequent to the training given the pilots in instrument flying, certainly as far as weather was concerned, almost 100 per cent of their flights were successfully accomplished.

It was the speaker's good fortune to bring the principles of instrument flying to the attention of Orville Wright, who within a few days brought them to the attention of airplane manufacturers and operating personnel who had gathered in New York City in conference. Strange as it seems, and while developed by Army officers on active duty, it was with difficulty that the flying fraternity and those in the Service particularly, accepted instrument flight. This robbed them of the belief that they flew by "feel of the ship" and by a God given sense which they believed themselves to possess and which others who failed in flying, lacked. Furthermore, they believed it violated every principle which they had been taught and that by accepting the same, they became what they termed "mechanical" or instrument flyers. This is exactly what those of us interested in the spread of this doctrine wished and something which has had its full fruition as the years have passed in that all flyers must now be adequately trained in instrument flight.

The speaker first met the then First Lieut. Ocker in 1920, when he already was interested in instrumentation. This officer was encouraged in his work and in later years many joint demonstrations were given by Capt. Ocker and myself, he demonstrating the aviational aspects of "blind flying" and I the physiologic. It was heartbreaking work, for while many listened, but few would accept these new ideas that now are accepted facts and must be known to all who pilot airplanes,

and without which knowledge, flying would still be in its swaddling clothes.

It was during the year of 1926 that the Air Commerce Act was passed by Congress. The medical aspects of aviation had reached such a status that it was deemed advisable, subsequent to passage of that act, to appoint a medical director under the Director of Aeronautics. After overcoming what seemed insuperable obstacles, the Department of Commerce appointed medical examiners all over the United States, and the thorough examination of private and student pilots as well as commercial and industrial pilots became a reality.

The following year, in May of 1927, Charles A. Lindbergh made his memorable flight from New York to Paris. He had had training in "blind flying" from Capt. Ocker and credits his successful flight to the knowledge of these principles and their application. This flight gave an impetus to aviation second to none and those who flocked to this new profession were in such numbers as to tax facilities of all kinds. The medical problems of the physician in connection with flying took on a new aspect. Flying at once became popular and the youth of the country taxed the abilities of the medical officers in the Service to make the necessary examinations, so avid were they to follow in the footsteps of their new found hero.

It must be remembered that at this time there were but few in civil medical practice who knew anything concerning flying, much less of the physical requirements necessary in this rapidly developing branch of transportation. Many of the Flight Surgeons, who had been graduated from the School of Aviation Medicine in prior years and had returned to their practices, were appointed to the position of examiners for the Department of Commerce. The awakening attitude of the public toward matters concerning aviation and a realization that further progress in the study of aviation medicine would be enhanced by the organization of a medical association devoted entirely to the study of this new specialty, brought about the organization of the Aero Medical Association of the United States in October 1929. This organization has for its object the advancement of the science and art of aviation medicine; a stimulation of inves-

tigation and study; a disseminating of knowledge concerning aviation and the establishment and maintenance of coöperation between the medical and other sciences concerned with aeronautical development and progress. It is the only organization of its kind. It is a lustily growing group that will wield increasing power in matters of aviation medicine.

Prior to this time, the School of Aviation Medicine of the Army was the only activity bearing the torch of medicine in aviation. It was now joined by a sister organization among those practicing this new type of medicine in civil life.

It was about this time that the speaker began some research work while stationed at the Materiel Division of the Air Corps at Wright Field, Dayton, Ohio. Here experimentation was on a very modest scale and was conducted in connection with the deleterious effects of noxious gases resultant from the combustion of gasoline and oils; the placing of corrective segments in goggles for those Air Corps officers who were becoming presbyopic; the study of what was later designated as aeroneurosis and researches into defective hearing as a result of airplane noises.

This meagre beginning came to fruition with the development of a physiologic research unit at Wright Field in 1935. At that time, it was the only laboratory doing any medical research work, primarily in connection with problems concerning aviation. With the organization of the physiologic research unit, a new chapter in aviation medicine was begun. The research work carried on by this laboratory had and now has for its solution, problems having to do almost exclusively with the pilot in the air—clothing, parachutes, helmets, masks, oxygen equipment, goggles, first aid packets, flak suits, electrically heated flying suits, dinghies and many other problems, the nature of which is confidential.

As must have been apparent in my discussion thus far, throughout the period 1917 to the present, the principal responsibility for the development of the medical aspects of aviation rested upon the doctor assigned to the Air Forces and who is known as the Flight Surgeon. Since the Flight Surgeon has assumed such an important place in the development of this

specialty of medicine and in the present war effort, with his duties assuming an ever increasing importance in the rapidly and marvellously expanded Air Forces, it might be well to speak briefly of him through whom the impetus for the modern advance and continuation in aviation medicine has been given. Even to the present, and no doubt, in this very audience, there are many who fail to realize or have never previously known, who and what a Flight Surgeon is.

He is a doctor assigned to Air Forces duty who must be a graduate of the School of Aviation Medicine and who must have fulfilled certain requirements with reference to length of service, to directed reading and evidenced his interest by actually engaging in flying. Professionally, he must have a solid foundation in general medicine complemented by a large fund of special knowledge. So equipped, he will have poise and dignity and his judgments will carry weight and his opinions will be respected. Furthermore, a Flight Surgeon so implemented will inspire confidence in flying personnel whom he has to examine and with whom he must be in the closest contact. He must be free from prejudice and show no favoritism. He must be courageous and be prepared to defend his opinions with facts and logic. His loyalty and integrity must be unquestioned. His understanding of human nature must be profound so that those with whom he associates will instinctively turn to him for guidance and advice. A good Flight Surgeon, as defined by me, therefore, must be a combination of an outstanding physician, priest and lawyer with a strong leaning toward the psychopathological side of medicine.

With the declaration of war, December 8, 1941, many laboratories in connection with medical schools took up the investigation of aeronautical problems and have been of tremendous assistance in the solution of these problems. Furthermore, the Naval Flight Surgeons' School organized in 1940 for the indoctrination of those going into naval aviation, is carrying out extensive research in connection with the problems incident to aviation and peculiar to that Service.

The National Defense Research Council has been active and has drawn some of the best medical minds of our country to the

solution of the problems sponsored by the Committee on Aviation Medicine.

The School of Aviation Medicine with the Aero Medical Laboratory, both functioning under the Air Surgeon of the Army Air Forces, have been in the forefront of all investigative and developmental work in connection with aviation to the present.

Although the primary purpose of the School of Aviation Medicine is that of training medical officers for duty with the Air Forces, it was inevitable that investigations of various types should be carried on at this school as well.

The School of Aviation Medicine throughout the years quietly had been attempting to solve some of the problems with which Flight Surgeons had been faced, albeit at times under the most serious of economic difficulties, studying the various effects of flight upon personnel and attempting to devise equipment to obviate these effects. However, its efforts were largely devoted to teaching; to its routine medical duties; to problems having to do with physical standards, and the faculty found itself engrossed in these, almost to the exclusion of all other considerations. The school also was occupied in developing Flight Surgeons for duty at the increasing number of Air Corps stations and stressed particularly the selection and physical care of Air Corps personnel.

Many of the physical standards in use today have evolved from previous standards due to the natural curiosity, development and research activity by members of the faculty and students, working throughout the years and at times at great odds and under severe handicaps. Following the declaration of war in World War II, and the tremendous development of the Army Air Forces, the need for a more elaborate department for the investigation of problems relating to the selection and maintenance of flying personnel became apparent. Late in the year, the creation of a research section of the School of Aviation Medicine was authorized and the laboratory was activated in January 1942.

This laboratory, in contrast with the one at the Materiel Division, Dayton, Ohio, has for its goal the solution of prob-

lems concerned with the selection of applicants for air crew training and for a determination, if possible, as to what physical and psychologic characteristics are necessary for those who would aspire to become pilot, bombardier or navigator. Physiologic research of a fundamental nature also is performed. Both laboratories are equipped with the very latest of research facilities with which to work.

The School of Aviation Medicine as now constituted consists of a Division of Teaching, Division of Research and a Division of Hospitalization. This sub-division is not as sharp as it might seem at first glance for most of the personnel of the Staff participate in any or all of the activities of the School, in their respective fields.

Progressive teaching institutions must frequently change their curricula to keep abreast of the times and project their studies so as to meet ever changing situations. This has been true of the School of Aviation Medicine since its inception.

The impact of war has had a tremendous effect on the life of the nation, which impact has been felt to its remotest corners. It has brought with it a whole train of significant events which too, in turn, have affected the school. Among these in aviation may be mentioned the progressive multiplication of the quantity, range and altitude of airplanes, the tremendous expansion in the numbers of Air Forces personnel; the world-wide theater of operations of the Army Air Forces and the consequent increase in the number of medical officers who have had to be trained to carry this additional burden.

During this war, the doctor in aviation certainly has performed outstandingly meritorious duty. Air evacuation of the sick and wounded, while sporadically performed before World War II, has come to full fruition and in some campaigns has been stated by Army commanders to have been a vital factor in the victories won. Through research, many problems have been solved that not only have been of outstanding value to the Air Forces but that will be applicable and useful in other lines of endeavor as well.

The modern system of the application of oxygen in high altitude flying is but an excellent example. The application

of the principle of pressurized cabins in substratosphere flying worked out in the Aero Medical Laboratory will do much for the comfort of aerial passengers in the postwar period, just as it now is bringing gratification and flying comfort to our B-29 pilots who are meting out death and destruction to the Japanese.

The development of the "flak suit" by a Flight Surgeon in 1943 has saved many lives in the war in Europe, now gloriously ended, and will continue to save lives wherever men go into aerial combat.

So one might go on specifying numberless contributions of the doctor to aviation, many of which have been due to the stimulation given by the School of Aviation Medicine that for the past quarter of a century, or the period of greatest progress in the history of aviation, has taken the lead in training the doctor for his duties with the art of flying. Those in command of this unique and outstanding school have realized, through the years, the importance of the medical man. It took years to bring his importance to the attention of Air Forces personnel as well as to commercial airlines. The value of the flying doctor to these services and the airlines is now well recognized and his place is secure. The public too demands this protection and is entitled to the same.

There are forces at work at this time which would undermine the firm position of the doctor in connection with flying, especially those physicians who have been specially trained in the proper selection and care of pilots. It is understood that the Civil Aeronautics Administration will put into effect, as of June 1st, a regulation that will permit any physician, the family physician who has no knowledge of the specialized type of examination required, to certify that a man is qualified for training leading to a "private pilot's" rating. This is devastating to all the efforts that have been expended in the past in attempting to indoctrinate the public, the industry and the Air Forces of the necessity of having only physically fit individuals flying. It is believed that forces are at work looking to the wide use of and the popularization of cheap airplanes in the postwar period. It would seem further that these same forces do not

wish their projects hampered by the restrictions of a formal physical examination. It must be remembered that this regulation has to do only with the private pilot and in no way brings with it a relaxation of military or commercial airline standards.

Possibly the picture is not as gloomy as it may at first seem, depending entirely on the restrictive legislation that may be passed limiting these sub-par flyers, as many will be, to certain definitely specified types of flying.

The Congressional Act specifies that every safeguard be thrown about those who fly "and to assure the highest degree of safety in aviation" (49 NSC 402b). This new attack would seem to be tearing down that which so patiently has been built up through the years in the interest of the public. However, and as it has occurred in the past, the doctor in aviation is stepping into the breach and will be the bulwark for the preservation of those who would fly.

There is more interest in aviation now than at any previous time and one needs but to read current trends in the press to visualize the tremendous postwar upswing in aerial travel. Let us not forget the doctor in aviation who has answered many of the problems that have made these marvelous advances possible.

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# THE CHALLENGE OF TOMORROW'S MEDICINE

WILLIAM H. MOURSUND*

*Mr. President, Regents, Dean Leake, Members of the Faculty, Members of the Graduating Classes, Ladies and Gentlemen:*

I bring to all most cordial greetings and felicitations from the Trustees, Faculty and students of Baylor University College of Medicine. As an alumnus of The University of Texas Medical Department I am deeply conscious and appreciative of the privilege and honor to be a part of these graduation exercises. Thirty-nine years ago it was my good fortune to have reached the same goal which you graduates have reached today. It has been my pleasure and satisfaction to have spent some thirty-four of those years in the field of medical education. To have witnessed and had a small part in the phenomenal advances made in all fields of medicine has been an interesting experience.

It is most gratifying to me, as it is, I know, to all affiliated with this institution, to contemplate the vast amount of service to humanity vested in this group of graduates in medicine, the largest graduating class in the history of the school. Nonetheless satisfying is the contemplation of the like service inherent in this class of graduates in nursing. All will render service for the betterment of mankind. That service will be of greatest value which results in producing and maintaining happiness. There is no factor more conducive to happiness than health.

It is indeed fitting that nurses and physicians should be graduates on the same occasion. There has always existed an interdependence of medicine and nursing. Nursing education and medical education, though inherently different, both seek the same ends, namely, the care, comfort and well-being of the sick and the prevention of disease and conservation

*Dean, Baylor University College of Medicine, Houston, Texas. Fifty-third Graduation Speaker, The University of Texas Medical Branch, Galveston, Texas, June 2, 1945.

of health. Whatever hampers one is deleterious to the other. History records that the profession of medicine has risen to eminence only during those epochs in which nursing has reached great heights.

Florence Nightingale defined nursing as "helping the patient to live." To this I would add "and helping the well to keep well." Although the major responsibility and duty of nursing remains the care of the sick, yet there has been expansion of service into many other fields. Florence Nightingale's contribution to the cause of health did not end with her memorable service in the Crimea nor later with her establishment of the first modern school of nursing. With another enthusiast, William Rathbone, she established the first visiting nurse service in history and this became, in a sense, the foundation of public health nursing. No movement has influenced and still is influencing so broadly the future welfare of the people as public health nursing in all its aspects.

Medicine, and I use the term in its very broadest sense, is founded in human sympathy. It is man for whom medicine exists. Its functions fully conceived must be to keep a whole people in health. But just to keep man free of disease is not enough. Public health is not the whole of life. A knowledge of rational human relationships is necessary. Unless successful solutions to some of the intricately complex and fast-growing problems of human relationship are found, we may have a world in which public health and medicine are of little significance. Technological skills and scientific knowledge are futile if political and social conditions prevent them from being used fully for the betterment of all mankind. There is no phase of life which is not touched by science. Though we live in a changing world, the principles and ideals governing the practice of medicine and nursing must always be those for the maintenance of the greatest service to humanity.

The medicine of tomorrow holds many challenging responsibilities of special concern for those engaged in medical and nursing education, research and practice. The heritage of medicine, made so noble by generations of men who sought unselfishly to create better health for each succeeding gener-

ation of our people, must be safeguarded in every way; yet the changing order, economic and social, will of necessity bring, as it already is doing, great innovations in medicine. There must be no interruption of the continuous efforts to improve and perfect the science and practice of medicine. There must be no compromise with quality. Of greatest importance to the patient is the assurance of a high standard of competence.

The known facts concering life and death, health and disease, have come as the slow accumulation of centuries of observation and study. We can have great pride in the recent advances: the synthesis of quinine; the rapid progress in chemotherapy, penicillin, plasma and sulfadrugs; the discovery of DDT, the potent insecticides; the progress in plastic surgery and others. Yet, there remain many important problems to which we must find the solution. There are numerous questions covering the early recognition of disease or diagnosis yet to be solved. Many problems of prevention exist on every hand. New methods of treatment are to be sought and tested. New drugs and chemicals are to be made or found in nature and their activity and value determined. Penicillin research alone has so stimulated interest in drugs produced by microorganisms that the discovery of 15 new substances of this kind has been reported recently. Investigators see a host of new medicines and related agents, including chemotherapeutic drugs, hormones, enzymes and amino-acids, outlined against the horizon of the future. It remains for you and others, through scientific investigation, to determine methods for their production and the extent of their usefulness in medicine.

As the veil of secrecy is lifted there emerges from the holocaust of this war a pattern of scientific marvels that staggers the imagination. There is scientific advancement on the one hand for the destruction of mankind, on the other, for the saving of human life. It is in the latter that we in medicine have primary concern. Never before have three years contributed so much to the annals of medicine. Never before has one branch of science struggled so hard to offset the ravages occasioned by others. Outstanding among scientific advances

brought into prominence by the present war is the control of communicable disease. Through advances in bacteriology and immunology, control has been achieved by vaccination for typhus, cholera, tetanus and yellow fever. In other instances, control has been accomplished by the application of proved public health measures as in mosquito and other insect control and water purification. We need only contemplate the present and future benefits from one discovery, DDT, in the control of those diseases in which the causative agent is transmitted by some form of insect life—malaria, typhus, etc.

No less outstanding are the advances in the treatment of disease and reduction of mortality. Penicillin, blood plasma and sulfa drugs have had their field of usefulness greatly enlarged through wartime needs with resultant saving of thousands of lives and favorably influencing the treatment and recovery of tens of thousands of our wartime casualties. Advances in plastic surgery are giving great relief to the physically handicapped. These, and no doubt, many more which will be disclosed as we go along the road to final recovery, are your heritage. You, who are just entering the various fields of medicine, will apply these advances for the maintenance of the health and happiness of the people whom you serve.

However, there remains a large number of so-called degenerative diseases among which are cancer, heart disease, kidney disease and disorders of the endocrine glands, which today are the chief causes of death and against which we have made little progress, offer an unlimited field for research and service.

We can neither become wholly absorbed with the future or forget the past. Each generation is prone to regard its own achievements as the pediment of the temple, unmindful of the fact that in terms of world history the accomplishments of one age are merely the foundation stones of the next. Let us take from the past the burning embers and go forward. Medicine is a progressive science. Yet we must not cast aside the old too hastily. When the Surgeon General of the United States Public Health Service made the statement that the average life span in the United States could be increased by ten years if merely all available health knowledge at the present

time were adequately utilized without the employment of a single new discovery, he did not, of course, mean that medicine should remain static or that new discoveries should be discouraged. His observation presented yet another problem to be solved, determination of the best means for making available to society as a whole the great mass of already existing knowledge applicable for the prevention of disease and the conservation of health. This problem can be solved in large measure by a comprehensive program of health education with close coöperation of the public and those engaged in the health fields. History records instances of the difficulty at times of convincing the public of the value of a particular health measure. Witness alone the time which expired between the discovery of vaccination against smallpox and its use as a public health measure. Other instances might easily be recited. Disasters such as epidemics and wars have at times produced a health conscious public and the adoption of certain preventive measures. During the Spanish-American War nearly one out of every five of the enlisted soldiers suffered from typhoid fever, thus the whole country at once became typhoid conscious. There resulted not only the adoption of measures for the control of typhoid but also for the control of other infectious diseases, particularly diphtheria and smallpox. There is every reason to believe that we can expect as comparable an increased acceleration of public health activities following the present war. Never before has a military personnel received such efficient and effective health and medical care as that afforded during this war. Never before has there returned to civilian life such a large number of health conscious people as will return after the termination of the present war. In the Army Medical Department there are over 500,000 enlisted men who have received practical training in sanitation and methods of caring for patients, and all the elementary skills required by the Army to protect the health and lives of men in its combat units. Like training has been received by large numbers of men in the other military branches. Most of the lessons learned in this training and from the accompanying experiences will be carried into

every community in this country. Not only these health workers but a large proportion of the troops they have served will return to their home communities convinced of the importance of preventive medicine. It can be predicted that this will have an important bearing on the future health of this country. Those in the various fields of medicine must coöperate fully with the public in making available to society as a whole the benefits that have accrued to our military personnel.

You, young men and women of the graduating classes, go forth today to play your part among fellow citizens. You are commencing. You are not a finished product. Unless you retain the capacity to learn, with all that that phrase implies, you will add little to the welfare of your fellowman and attain but small success for yourself. If you achieve success it will be in a measure due to the help of your associates. No man can live alone. We are the servants of each other. We are under constant and lasting obligations to one another. We owe loyalty to friends, to our organizations, to our country and to our God. I bid you go forth then into the strenuous life of this country, loyal, honest and aggressive. I ask you to remember always that you are members of The University of Texas family, and that the standards, the ideals and mottoes of The University of Texas are yours to keep in honor before the world in all your activities. Not alone the eyes of Texas but of all the world are upon you. May each of you have a long life abundantly endowed with opportunities for those services to mankind which your profession imposes upon you as a sacred trust. I bid you Godspeed and may you have complete success in all your efforts for the betterment of mankind.

# RETICULO-ENDOTHELIAL IMMUNE SERUM (REIS)

## II. Preliminary experiments on its stimulating action on chick heart fragments *in vitro**

C. M. POMERAT

Restriction of outgrowth and clumping of migrating cells from splenic fragments in tissue culture medium containing strong concentrations of REIS have been recently demonstrated (Pomerat and Anigstein, 1945 a). Using similar techniques, outgrowth from heart fragments was found to be completely inhibited in the presence of homologous REIS at a concentration of 1:4 (Pomerat and Anigstein, 1945 b). Damaging effects from the use of high dosages of REIS *in vivo* also have been established. Intraperitoneal injection of 1 cc. of anti-rat serum produced marked anemia and uncovered an acute bartonellosis in rats which were latent carriers of this infection (Anigstein and Pomerat, 1945 a). This effect was not produced when heretologous (anti-chick and anti-guinea pig) serum was used at corresponding dosage (Anigstein and Pomerat, 1945 b).

While strong concentrations of such sera have inhibitory (blockading) action on the connective tissue system, exceedingly small doses (0.03 to 0.10 cc. of a 1:100 anti-reticular cytotoxic serum with a complement fixation titer of 1:100–1:240) recommended by Soviet workers for human therapy are said to have a directly opposite effect. According to Bogomolets (1943), even the blockading doses "are many times smaller than those of antitoxic and bactericidal serums."

Demonstration of the stimulating action of sera prepared in our laboratories by *in vitro* methods thus far has proved difficult. Nevertheless, the importance of this direction of research in promoting the practical use of immune sera has convinced us

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of the need for publishing results obtained from preliminary experiments.

Assistance in estimating the reliability of the data was generously given by Dr. J. A. Scott and Miss G. L. Levy. The authors wish to express their sincere thanks to Mrs. Madeline Lay for invaluable technical assistance.

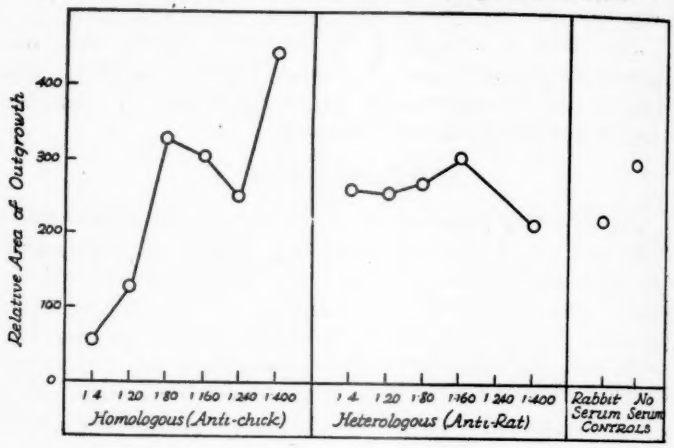
## Experimental Results

Hanging drop preparations of 6-day chick hearts were made with the use of medium containing 2 parts of heparinized rooster plasma, 1 part of 12 per cent chick embryonic extract and 1 part of varying concentrations of anti-chick (homologous) and anti-rat (heterologous) REIS. Sixteen preparations were made for each type of sera at dilutions of 1:4, 1:20, 1:80, 1:160, 1:240 and 1:400. In addition, controls were made which contained normal rabbit serum at dilutions of 1:4 and others containing no mammalian sera.

Living cultures were projected at a magnification of 40 diameters of ¼ inch graph paper and the number of squares covered by the projection were counted. The values obtained were used to compare the relative outgrowth represented for cultures after five days of incubation at 37.5 C., and are represented in figure 1. Inhibition was observed for heart fragments in homologous but not in heterologous serum at concentrations of 1:4 and 1:20. These results confirm those reported for spleen fragments (Pomerat and Anigstein, 1945 a). Values for the outgrowth of cells from fragments of chick heart in medium containing a concentration of 1:400 of homologous serum suggested a stimulatory action. This was not found for corresponding concentrations of heterologous (anti-rat) serum with approximately the same complement fixation titre.

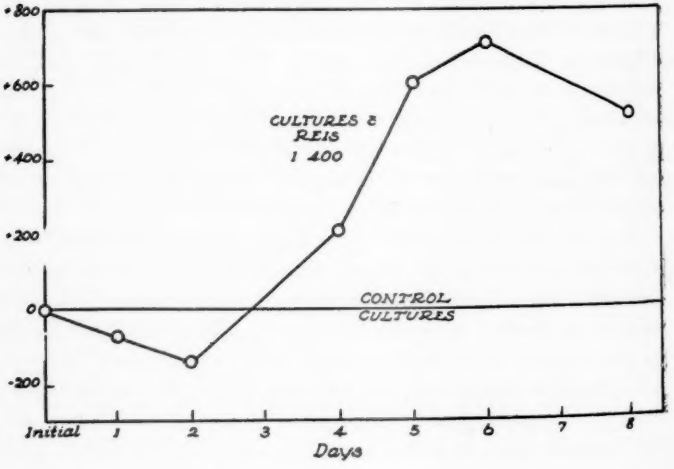
In a second series of hanging drop cultures, medium containing a 1:400 dilution of anti-chick REIS with a complement fixation titre of 1:1200 was compared with control clots containing a similar dilution of normal rabbit serum. Daily pencil outlines on a good grade of bond paper were made of projections of living cultures for eight days. The areas represented were cut out and weighed. Corrections were made for the magnification and data were assembled for the actual area

Fig. I. Effect of REIS on Chick Heart Fragments in vitro




of outgrowth of 33 experimental and control cultures. Results are represented most advantageously by showing the percentage difference between treated and untreated cultures as seen in figure II. After an initial depression the average area of

Fig. II Average % Difference in Area of 33 Chick Hearts



treated cultures showed a marked superiority in outgrowth over controls by the sixth day. It should be noted that the standard errors of the differences between control and experimental values on any given day were rather high, but the differences between the averages were consistently in the same direction. Moreover, it would be more appropriate to test the significance of the difference between the growth rates of the 2 series. Although this test has not yet been completed, it appears highly probably that the difference is statistically significant.

In another series of experiments, Carrel flasks were utilized. As a medium in which 3 or 4 heart fragments from 6-day old chicks were imbedded, 0.2 cc. of rooster plasma and 0.6 cc. of 5 per cent chick embryonic extract was used in 20 flasks. One-half of the flasks were treated with a supernate consisting of 0.75 cc. of 1–400 anti-chick REIS, while a similar volume of 1–400 rabbit serum was introduced into the remainder.

The area of outgrowth in cultures treated with the REIS was significantly retarded (figure III). It was obvious that even though the concentration and titre was the same as that used in hanging drop preparations, the relative dosage in the supernatant fluid of the Carrel flask was greater. On the eighth day the supernatant was removed and both REIS and control cultures were divided into three groups. These received 3 different supernatural fluids: (1) Tyrode's solution; (2) 5 per cent embryonic extract; and (3) 25 per cent embryonic extract. No difference was seen between cultures receiving Tyrode alone (figure IV a), irrespective of previous treatment. In contrast to controls, the addition of weak embryonic extract produced little effect on cultures previously treated with REIS (figure IV b). Considerably greater response, however, was obtained in the REIS series following the addition of supernate containing 25 per cent embryonic extract (figure V). While the number of cultures was small, the possibility that REIS may have made cells more susceptible to the growth promoting properties of strong embryonic extract is worth further study.

Measurements of the outgrowth from explants *in vitro* do not necessarily represent true growth (Parker, 1938). The

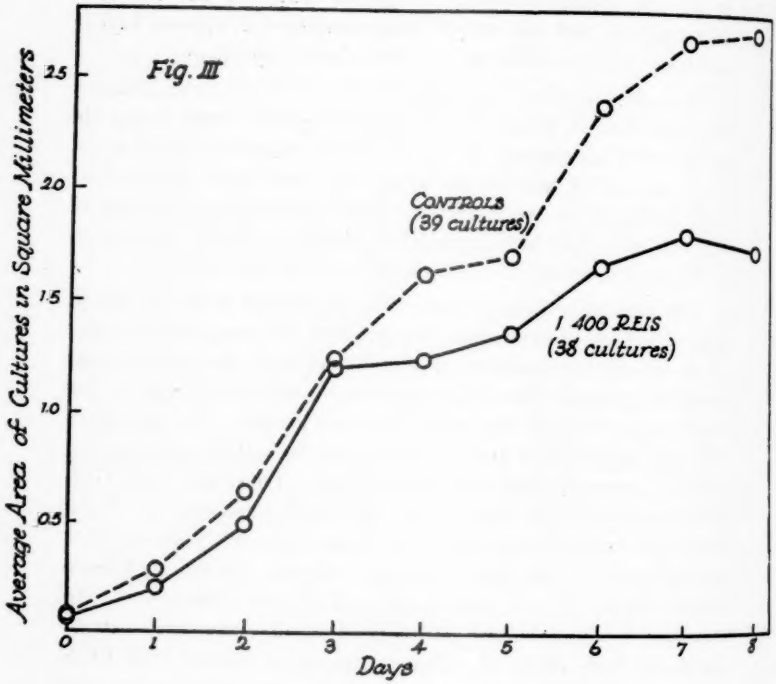


Fig. III
Average Area of Cultures in Square Millimeters
2.5
2.0
1.5
1.0
0.5
0
1
2
3
4
5
6
7
8
Days
CONTROLS
(39 cultures)
1 400 REIS
(38 cultures)

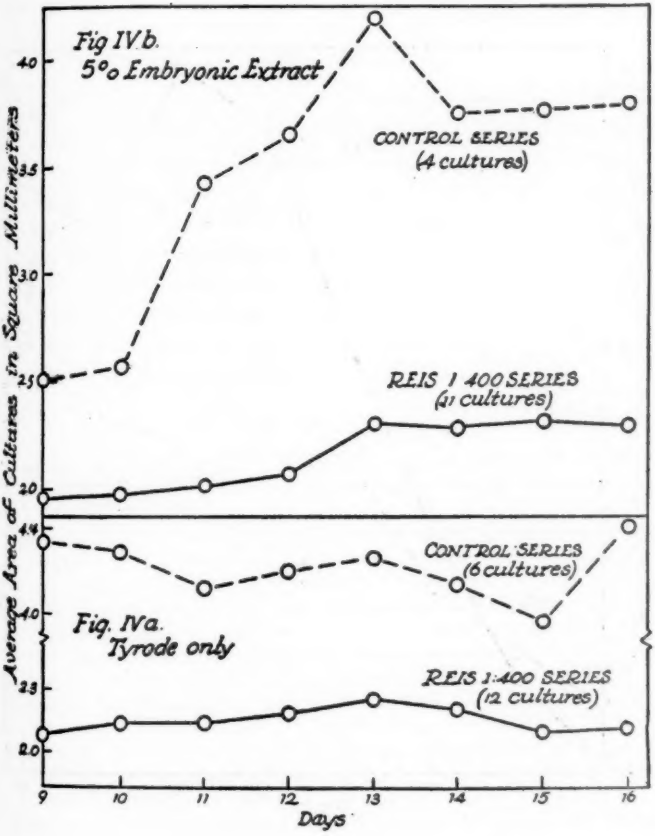


Fig IV b.
5% Embryonic Extract
CONTROL SERIES
(4 cultures)
REIS 1 400 SERIES
(11 cultures)
CONTROL SERIES
(6 cultures)
Fig. IV a.
Tyrode only
REIS 1:400 SERIES
(12 cultures)
Average Area of Cultures in Square Millimeters
Days

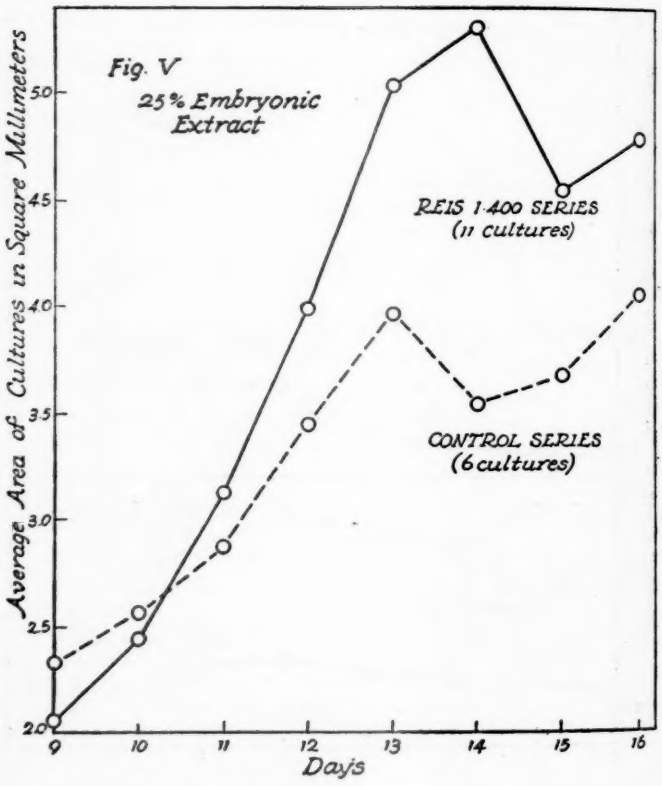


Fig. V
25% Embryonic Extract
REIS 1-400 SERIES (11 cultures)
CONTROL SERIES (6 cultures)
Average Area of Cultures in Square Millimeters
5.0
4.5
4.0
3.5
3.0
2.5
2.0
9
10
11
12
13
14
15
16
Days

method of computing the mitotic index which has been perfected by Willmer (1935) and the use of roller tube cultures (Gey and Gey, 1936) for biochemical studies offers promise for further investigations on the stimulating effect of REIS.

SUMMARY

Heterologous (anti-rat) REIS gave no evidence of inhibiting or stimulating outgrowths from chick heart fragments *in vitro*. On the other hand, homologous (anti-chick) REIS, having a complement fixation titre of 1:1200, inhibited outgrowth in hanging drop preparations at a concentration of 1:4 and 1:20 while at 1:400 some evidence of stimulation was observed. When used as the supernatant fluid at the same concentration such serum proved somewhat inhibitory but cultures so treated showed stimulation in excess of controls following subsequent treatment with strong embryonic extract.

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Gey, G. O., and Gey, M. K.: The maintenance of human normal cells and tumor cells in continuous culture. I. Preliminary report: Cultivation of mesoblastic tumors and normal tissue and notes on methods of cultivation, Am. J. Cancer, *27*:45–76, 1936.

Parker, R. C.: Methods of Tissue Culture, New York, Paul B. Hoeber, Inc., 1938.

Pomerat, C. M., and Anigstein, L.: Reticulo-endothelial immune serum (REIS). I. Its action on spleen *in vitro*., Texas Rep. Biol. & Med., 3:122–141, 1945 a.

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Willmer, N.: Tissue Culture, London, Methuen and Co., 1935.

# CALLING ATTENTION TO:

## Items of Possible Interest to Friends of Our Effort

Joyful (?) June, 1945

1. Books Can Be Peaceful, Too: E. Huntington's *Mainsprings of Civilization* might help San Francisco conferees (Wiley, N.Y., 16, 660 pp. $4.75, 1945). R. R. Grinker & J. R. Spiegel's *Men Under Stress In and After Combat* may also be helpful for the harder problems of peace (Blakiston, Phila. 5, $5, 1945). Harvard Press announces important new ones: R. J. Dubos's *Bacterial Cell* (500 p., $5, 1945); C. K. Drinker's *Pulmonary Edema and Inflammation* (200 p., $3, 1945), and F. M. Burnet's *Virus as Organism; Evolutionary and Ecological Aspects of Some Human Virus Diseases* (150 p., $2, 1945). Spot-lighting the importance of word-symbols is George Stewart's fine *Names on the Land* (Random, N.Y., $3, 1945). J. N. Lott and R. H. Gray offer *Law in Medical and Dental Practice* (Foundation Press, Chicago 6, 499 p., $4.75, 1945). P. DeKruif finally shows his age in *The Male Harmone* (Harcourt, N.Y., 243 p., $2.50, 1945). It is now Henry Schuman who goes to town: T. E. Keys' important *History of Surgical Anesthesia* (244 p., $6, 1945); J. M. D. Olmsted's definitive *Francois Magendie* (304 p., $5, 1945); W. Beaumont's *Two Diaries* (ed. G. Miller, 144 p., $6, 1945); Index to the *Annals of Medical History* (most worthy tribute to F. R. Packard, out Nov. 1, $10); a new edition of M. Frank's translation of L. Choulant's *History and Bibliography of Anatomic Illustration* (435 p., $12, 1945), and a new quarterly *Journal of the History of Medicine* (first issue, Jan., 1946, $7.50). Henry really is going places: see his delightful shop at 20 E. 70, N.Y., 21. M. G. Wohl edits excellent *Dietothrapy* (Saunders, Phila. 5, 1029 p., $10, 1945). W. Haymaker & B. Woodhall of Army Inst. Pathology offer useful *Peripheral Nerve Injuries* (Saunders, 227 p., $4.50, 1945). Macmillan announces serial publication of H. Gold & M. Cattell's *Cornell Conferences on Therapy*. To the Hoeber medical student series edited by Fred Zapffe have now been added D. Mainland's *Anatomy as a Basis for Medical and Dental Practice*, and C. H. Thienes' *Fundamentals of Pharmacology* (P. B. Hoeber, N.Y., 16, $7.50 and $5.75, 1945). R. P. Wodehouse offers *Hayfever Plants* (Chronica Botanica, Waltham, Mass., $4.75, 1945).

2. Pharmacology Items: F. Hawking gives informative review of recent work on pharmacology of sulfonamides (*British Med. Jr.*, 1:505, Apr. 14, 1945). R. L. Vollum & G. S. Wilson report that sulfonamide lozenges are of no value in preventing streptococcal sore throat epidemics (*Brit. Med. J.*, 1:545, Apr. 21, 1945). P. K. Knoefel & G. Lehmann note behavior of gelatin fractions in body, finding rate of urinary excretion varying inversely with molecular weight (*J. Pharmacol. Exp. Therap.*, 83:185, 1945). R. J. Schachter shows that IV injections of 5,000 units

of cholinesterase alleviate symptoms of traumatic shock (*Am. J. Physiol.*, 143:552, 1945). C. H. Li & V. V. Herring report that adrenocorticotropic hormone helps rats resist anoxia (*Ibid.*, p. 548). F. K. Bell & J. C. Krantz propose reasonable chemical assay for digitalis (*J. Pharmacol. Exp. Therap.*, 83:213, 1945). K. Dixon shows that penicillin inhibits fibrinolysis (*Brit. Med. J.*, 514, Apr. 14, 1945).

3. Toxicology Items: C. H. Clarke, H. Wyers, E. C. Butler & Co. offer helpful symposium on methyl bromide poisoning (*Brit. J. Indust. Med.*, 2:17–31, 1945). R. Lemberg & J. P. Callaghan find nearly half intake of TNT through skin or mouth is excreted in urine as aromatic amines with evidence of storage and destruction in body by reduction (*Austral. J. Exp. Biol. Med.*, 23:6, 1945). W. H. Forbes, F. Sargent & F. J. Roughton study rate of CO uptake, rate of CO reaction with Hb, and average time spent by blood in lung capillaries (*Am. J. Physiol.*, 143: 594–621, 1945).

4. Odds and Items: English scientists as usual rise to the occasion with a splendid anonymous tribute to President Roosevelt (*Nature*, 155, 475, Apr. 21, 1945). Z. Vaz & Co. (Brazil) recommend calcium gluconate in prevention and treatment of DDT poisoning (*Science*, 101:434, Apr. 27, 1945). I. W. Sizer & C. E. Prokesch suggest tyrosinase for inactivation of poison ivy irritants (*Ibid.*, p. 517, May 18). G. N. Papanicolaou & V. F. Marshall describe urine sediment smear diagnostic test for cancer of urinary tract (*Ibid.*, p. 519). G. Holmes gives excellent Royal Society Ferrier Lecture on organization of visual cortex in man with point to point representation of retina in striate area (*Proc. Roy. Soc.*, B, 132: 348, 1945). P. Weiss & Co. find distal flow of few mm/hr of endoneurial fluid around peripheral nerves (*Am. J. Physiol.*, 143:521, 1945). H. M. Turnbull Festschrift contains L. D. Parsons' note on amyloid infiltration of liver and spleen from pentose nucleoctide injection and S. T. Callender & Co.'s finding that RBC average life is 120 days and that normal rate of replacement is 0.83% per day (*J. Path. and Bact.*, 57:9, 129, 1945).

### July, 1945

1. Notes on Books: In addition to Tom Keys' fine and finely illustrated account of *The History of Surgical Anesthesia*, the volume contains an excellent essay by Noel Gillespie pointed to the future, and a neat bibliographical account of Morton items by John Fulton (Schuman's, 20 E. 70, N.Y. 21, $6, 1945). D. T. Starnes edition of W. Clowes' *Booke of Medical Observations* (1596) is interesting but poorly lithoprinted (Scholar's Facsimiles and Reprints, N.Y., 1945). Another well illustrated pertinent survey is N. Taylor's *Cinchone in Java* (87 pp., Greenberg, N.Y., $2.50, 1945). J. Wiley, 440 4th Ave., N.Y. 16, offers R. S. Bates' *Scientific Societies in the United States* at $3.50 and A. L. & K. B. Winton's *Analysis of Foods* at $12. W. B. Cannon stimulatingly discusses *The Way of an Investigator: A Scientist's Experiences in Medical Research*, in summing up his fruitful years (W. W. Norton, 70 5th Ave., N.Y. 11, 229 pp.,

$3, 1945). A. Kardiner studies *The Individual and His Society: The Psyco dynamics of Primitive Social Organization* (Columbia Univ. Press, 305 pp., $4, 1945). Important for book publication is R. J. Henry's *Mode of Action of Sulfonamides*, a fine critical review with 698 references (Publ. Josiah Macy, Jr., Foundation, Review Series, 2:1–285, 1944). Note *Report of Survey of Medical Records Created by Federal Government* (National Research Counc., 180 pp., Washington, 1945).

2. NOTES ON SYMPOSIA: Otherwise helpful symposium on sympathomimetic agents held by American Chemical Society (*Ind. Eng. Chem.*, 37: 116–151, 1945) is unbalanced by failure to include summary by Gordon Alles. R. J. Williams & Co. issue interesting series of Cancer Studies (*Univ. Texas Publ.*, No. 4507, Austin, 1945) with articles on virus-like tumor agent by A. Taylor and tumor effects on Hb by R. E. Hungate. R. A. Willis offers stimulating review of recent advances in experimental production of tumors (*Med. J. Austral.*, 1:361, Apr. 14, 1945). About 600 reports in 1945 Federation Proceedings ranging from H. W. Ades on the corpus callosum to C. Weiss & N. Halliday on tuberculo-carbohydrates and phosphates (*Fed. Proc.*, 4:1–166, 1945), of which fair share is Blakian!

3. SUMMER SIMMERINGS: H. A. Howe tells why it doesn't help to be afraid of polio in an excellent summary of curent thought (*Harper's*, 190:646, June, 1945). D. Ludwig offers a pertinent and well documented review on effects of atmospheric humidity on animal life (*Physiol. Zool.*, 18:103–135, 1945). T. F. Rose discusses urinary colic due to crystalluria and calculi in hot humid climates (*Med. J. Austral.*, 1:558, June 2, 1945). C. P. Mathe neatly reviews differential diagnosis and treatment of anuria (*Urol. Cutan. Rev.*, 49:223, 1945). R. M. Stecher makes a pleasant plea for more light (*Bull. Med. Lib. Asso.*, 33:220, 1945).

4. NOTES ON BODY COMPOSITION: H. H. Mitchell & Co. discuss chemical composition of adult human body with reference to calcium and its bearing on biochemistry of growth, finding subjects vary by 25%, and that much calcium is lost by sweating (*J. Biol. Chem.*, 158:625, 1945). E. N. Rathbun, N. Pace & Co. find female body averages 4.7% more fat than male; water averages 72.4% fat free body mass with standard deviation of 2.1%; chemically combined nitrogen averages 3.5% lean body mass, standard deviation 0.27%; lean body mass relatively constant, with fat as a diluent (*Ibid.*, p. 667–691). L. Arnold & Co. report general health and mental performance, but not physical prowess, is superior in good eater as compared with bad eaters in 7 year olds (*S. Afr. J. Med. Sci.*, 10:9, 1945).

5. NOTES: J. K. W. Ferguson & L. P. Dugal note RQ of expired air may be used to calculate relations between $CO_2$ and $O_2$ tensions in alveolar air (*Canad. J. Res. Med. Sci.*, 23:32, 1945). H. Koteen gives encouraging survey of lumphogranloma venereum (*Med.*, 24:1, 1945). F. C. Warring proposes estimation of ratio of maximum lung ventilation to walking ventilation as a guide to thorocoplasty (*Amer. Rev. Tb.*,

51:432, 1945). A. Lacassagne & Co. of reviving Paris find that application of weak carcinogenic hydrocarbons inhibits subsequent action of strong carcinogens of like molecular structure, by blocking (*Brit. J. Exp. Path.*, 26:5, 1945). A. K. Janes recommends 2 mgm carbaminoylcholine thrice or more daily to reduce migraine attacks (*Bris. Med. J.*, 1:663, May 12, 1945). E. J. Boell reports that nerve degeneration results in marked reduction in choline esterase activity (*J. Cell. Comp. Physiol.*, 25:75, 1945). H. Hartridge discusses change from trichromatic to dichromatic vision in human retina (*Nature*, 155:657, June 2, 1945).

MIDSUMMER, 1945

1. ON THE SOCIOLOGICAL FRONT: Worth reading is L. Mumford's *City Development: Studies in Disintegration and Renewal;* maybe Honolulu should have followed Mumford's advice (Harcourt, Brace, N.Y., 248 pp., $2, '45). B. Malinowski analyses *The Dynamics of Culture Change* (Yale Press, New Haven, 171 pp., $2.50, '45). Laura Thompson and Alice Joseph discuss *The Hopi Way* (to peace), and note high IQ of Hopi children (Univ. Chicago Press, 151 pp., $3, '45). D. Abrahamsen dilates on *Crime and the Human Mind* (Columbia Univ. Press, N.Y., 244 pp., $3, '44). Do you know the Social Work Year Books? 8th issue, '45, edited by R. H. Kurtz, 620 pp., at $3.25, from Russell Sage Foundation, N.Y. Along the usual line is O. S. English and G. H. J. Pearson's *Emotional Problems of Living: Avoiding the Neurotic Pattern* (Norton, N.Y., 438 pp., $5, '45). M. F. A. Montagu concludes that intelligence tests at last war show correlation with socio-economic history (Amer. J. Psych., 58:161, '45). J. N. Morris examines health of 440 millions in India, in light of population crisis, and sees little hope (*Lancet*, 1:743, June 16, '45). V. Bush looks at tomorrow, bravely speculating on how we may think mechanically with logic machines (*Atlantic*, 176:101, July '45). And what is your idea of Federal subsidy for scientific work? C. Binger gives excellent and brief popularization of *The Doctor's Job* (Norton, N.Y., $3.50, '45).

2. ON CELLS AND TISSUES: R. Hober offers important *Physical Chemistry of Cells and Tissues* (Blakiston, Phila., 5, $9, '45). Volume 5 of *Advances in Enzymology and Related Subjects* is edited by F. F. Nord and C. H. Werkman (Interscience Publ., N.Y., 268 pp., $5.50, '45). E. Schrodinger also asks *What is Life?* (Macmillan, N.Y., 91 pp., $1.75, '45). R. A. Moore edits Volume 11 of Biological Symposia on *Ageing and Degenerative Diseases* (Cattell Press, Lancaster, Pa., 242 pp., $3, '45). R. A. Moore also offers new text on Pathology (W. B. Saunders, Phila. 5, 1338 pp., $10, '45).

3. ON ANTIBIOTICS: L. F. Moldavsky & Co. of Harmon Gen. Hosp. warn against danger of thrombus formation with high doses of penicillin and suggest its use as a coagulant in hemorrhagic diseases (*Science*, 102:38, July 13, '45). L. Loewe & Co. report plasma conc. of p-aminohippuric acid of 10 mgm/100 cc. (non-toxic) greatly prolongs penicillin action (*Proc. Soc. Exper. Biol. Med.*, 58, 298, '45). J. T. Weld notes antibiotic action of extracts of Tillandsia usneoides (spanish moss) (*Ibid.*, 59:40,

'45). J. A. Herrick observes fungicidal action of clavacin (*Ibid.*, p. 41). D. Jones & Co. find evidence for antiviral action of actinomycin A (*Science*, 101:665, June 29, '45). D. Perlstein & Co. propose urinary estimation of glucuronic acid as measure of penicillin absorption (*Science*, 101:562, June 1, '45). W. F. Elias and J. Durso note little absorption of streptomycin from gut and possible presence of body inhibitor (*Ibid.*, p. 589, June 8, '45). S. Waksman proposes excellent method for standardization of streptomycin (*Science*, 102:40, July 13, '45). W. M. M. Kirby describes properties of penicillin inactivator from penicillin resistant Staph. (*J. Clin. Invest.*, 24:165–175, '45).

4. On Hormones: Just noted is comprehensive discussion of synthetic hormones by G. Masson (*Rev. Canad. Biol.*, 3:491–582, '44). J. P. Chu and S. S. You (Chengtu) offer evidence that follicle stimulating and luteinizing hormones of pituitary are under direct regulation of thyroid (*J. Endocrin.*, 4:115, '45). J. E. Caldwell & Co. find specific agent in bone marrow able to stimulate leucopoicsiz in benzene poisoned rabbits (*Am. J. Med. Sci.*, 209:717, '45). I. J. Kligler & Co. observe that environmental change from dry to humid with constant temperature activates thyroid, explaining our pep at Galveston! (*Proc. Soc. Exper. Biol. Med.*, 58:286, '45).

5. On Varia: E. A. Stead, Jr., & Co. report neat studies on cardiac output (*J. Clin. Invest.*, 24:326–344, '45). A. M. Martinex offers full survey of leucocyte variations in pulmonary Tb (*Publ. Cent. Invest. Tisiol.*, 8:281–420, '45). C. Torda and H. G. Wolff claim muscle fatigue may be result of decrease in local synthesis of acetyl-choline during prolonged muscle contractions (*Proc. Soc. Exper. Biol. Med.*, 59:13, '45). P. A. Neal & Co. report fully on low toxicity and potential danger of aerosols containing DDT (Supplements No. 177 and 183 to *Pub. Health Rep.*, Washington, '45). J. M. Schneck offers interesting bibliography on bibliotherapy (Psychiatrists, please note!) and hospital libraries (*Bull. Med. Lib. Asso.*, 33:341, '45). G. King and L. T. Ride correlate thiamine deficiency with pregnancy toxemia (*J. Obs. Gyn. Brit. Emp.*, 52:130, '45). C. P. G. Wakeley skillfully analyses effects of underwater explosions on human body (*Lancet*, 1:715, June 9, '45).